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NORMAL AND PATHOLOGICAL PHYSIOLOGY OF BONE

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THE NORMAL AND PATHOLOGICAL PHYSIOLOGY OF BONE

ITS PROBLEMS

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ILLUSTRATED

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PREFACE

This book is the fruit of ten years of collaboration.

For ten years we have unceasingly observed the numerous aspects of the normal and pathological evolution of bone, have reflected on the problems to which they give rise, and have sought the various solutions in every direction, through histology, radiography, experiment, and direct observation on man, each of us using for that purpose his particular field and pouring into a common fund the result of his own observations.

Thus, little by little, we have been forced to a new understanding of everything concerned with the development, life, evolution, diseases, and regeneration of bone.

It seemed to us that the time had arrived for an exposition of the synthesis of those things which we had observed and deduced.

Certain individuals will perhaps think that it would have been preferable to have been more analytic and more documentary, to have confined ourselves to explaining facts without making a constructive effort, thus permitting others to draw their own conclusions in such a complex matter. It is the old quarrel of objective and subjective literature.

We are frankly prejudiced.

Having ourselves tried to penetrate the meaning of things, we shall show how one may understand today the intimate construction of bone. Claudel has said somewhere: "Do not trust thine eye alone, but without reserve, all that is thyself." (N'applique point à la vérité l'oeil seul, mais tout cela sans réserve qui est toi-même.)

This we have done, persuaded that it is legitimate to choose one's opinion even though it is no longer in harmony with contemporary views.

Medical works of our time too frequently have the appearance of manuals of history or anthology. They should be a critical and systematic exposition of actual science.

Like Louis XI kissing the figures on his hat each time he uncovered himself, we have thought ourselves obliged to salute our predecessors, each time we have uncovered ourselves, without daring to make the choice of separating the good grain from the tares.

Then, this done, without reaching the bottom of things, we have placed in juxtaposition in parallel lines facts and theories, without condensation, without reaching a conclusion, without showing frankly the extent of our ignorance.

It would be well to end the poor method of popularization which retards progress.

Without doubt, in criticizing the past one exposes oneself to criticism. It matters little. All loyal pursuit of truth brings one nearer to it even if one does not attain it.

Certainly facts are facts and we should not forget the past, on the edifice of which we have elevated ourselves in order to advance in our own time; but, in this past we should make a choice instead of continually musing on outworn dogmas. When a thing is indeed dead, let us say so, and do not allow a doubt to linger on with the possibility of its revival.

In the question of osteogenesis, masses of observations and experiments have been accumulating for a long time. Every day the problem instead of becoming simpler becomes more complex. After having indicated what has been accomplished, there is perhaps some utility in stating clearly the problems, the solutions of which should be sought.

This book was conceived in this spirit. For ten years we have read everything that we could procure on the subject of osteogenesis. We have retained that which seemed good to us, comparing it with our own observations.

That which has been revealed to us by this work is set forth here, the whole having a unity, so to speak, which gives rise to a theory.

This theory is of a general character. It applies to all the modalities of osteogenesis. It allows an understanding of its diverse peculiarities. It explains disconnected and obscure pathological facts.

It always takes into consideration the individual tissues themselves, and not their relationship to the whole individual. The phenomena of the life of tissues are automatic. They mutually reveal themselves, as in a stream. One runs a great risk of a mistake in interpreting them otherwise.

One need not be surprised to find, in the course of these pages, sentences like the following: "This question is absolutely unknown," "The problem is entirely unsolved," etc. We should consider that we had fulfilled one of the prime objects we have in view if this book can place some one on the road to fruitful researches.

The problem of osteogenesis has passed through many phases. It has been histological, and surgical, and the present time it is above all chemical. It is useless now for the histologists to repeat what has been done so many times, and for the surgeons to exeriment on the periosteum, on grafts, and on the osteogenesis of repair. It is now the turn of the chemists and physicists. They alone can open up new horizons by giving us some of the certainties we lack. When they have solved certain pending questions, it will be possible to resume with profit the studies of the past. We can then progress, and, perhaps, have bone formed at will, accelerate the union of fractures, and prevent the pathological and physiological rarefactions of bone. But for this to occur, it is necessary for us to ask them definite questions.

We shall often see in the course of these pages how much the division into water-tight compartments, which always prevails in the biological sciences, has impeded the progress toward knowledge.

We have tried to establish connections and to indicate clearly the problems which it is necessary to solve before progress can be made.

This book is dedicated to Ollier.

We did not know Ollier. We were not his pupils. We have often been called on to contradict him. After having proved the exactness of the facts that he had observed, we have finally overthrown his theories.

Nevertheless, it seems to us that, were he still living, he would understand us. In any case, we have tried to follow his spirit and to guide ourselves by his method, considering him above all as one of the originators of contemporary scientific surgery.

Villerest-sur-Loire.

INTRODUCTION TO ENGLISH TRANSLATION

In the vast literature dealing with bone there is much that is obscure, unknown, and mysterious. Especially is this true of its physiology. The complexities of this are great because the facts have not been gathered together, assorted, arranged in relationship to each other, and condensed in a concise manner. Professors Leriche and Policard have envisioned this condition, have surveyed the entire fund of knowledge pertaining to bone, condensed it, discarded that which was inaccurate and, as they say in their introduction, formed a synthesis of their study and observation which permits one to state the *problems* which are the foundation of bone physiology. The contributions which these authorities have made in the past are now fortunately combined in compact form in this monograph, "The Normal and Pathological Physiology of Bone, Its Problems." This book is welcome and stimulating. It is one which has been needed for a long time by those whose activities may in any way bring them into the field of bone physiology and pathology.

This work should prove so useful to the orthopedic surgeon, the general surgeon, the orthodontist, and, above all, the radiologist, that we felt that the scope of its readers should be extended beyond that which would be the case did it remain in the original. Therefore, we have undertaken this translation, which we trust will prove as helpful to others as it has been to us in understanding the protean aspects of the physiology of bone. French, with its complex shades of meaning, rendered this translation into English most difficult. We have striven faithfully to reproduce precise meanings from the original, a difficult task; we trust, however, that the reader will appreciate this fact and overlook departures from good usage.

As the authors state in their introduction, some of their hypotheses or views will meet with disagreement. Whatever one's ideas may be in regard to them, it must be conceded that they have presented fairly the points of disagreement with their own views. The translators are in accord with Professors Leriche and Policard in principle throughout, though differing to some extent in regard to details. Where this has been true the divergence of views is embodied in footnotes which are initialed by one or the other of the translators. They have similarly added such facts as seemed pertinent which have appeared since the publication of the original.

This translation is presented to the profession with the hope that it will accomplish the result referred to by the authors in their introduction, that is, the stimulation of research in the directions in which they point out knowledge needs to be gained. We would particularly emphasize the importance and value of the authors' belief that the future development of our knowledge in this field will be derived from physical and physicochemical investigation. We believe with them also that until certain fundamental points in this direction have been settled, certain modes of investigation must remain at a standstill.

We wish to express our gratitude to Professors Leriche and Policard for permitting us to translate their remarkable work.

S. M.
J. A. K.

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CHAPTER I

THE SIGNIFICANCE OF BONE TISSUE AND THE GENERAL COURSE OF OSSIFICATION

Before we discuss in detail the general processes which govern the physiology of bone, it is important to stress several fundamental facts of the general biology of this tissue and the general process of ossification.

I. THE GENERAL IDEAS PERTAINING TO BONE TISSUE

Toward the middle of the nineteenth century, an idea of great fertility was advanced by the histologist Reichert. In a broad conception of the tissues of the organism, this author demonstrated that bone and cartilaginous tissue should be considered as derivatives by adaptation from connective tissue. Since his time, in bone as well as in cartilage, we have been able to establish the essential feature of connective tissue: the collagen material, a substance which by boiling or hydrolysis produces gelatine, or "glue." Bone and cartilage, tendon, or adipose tissue, are derivatives of this connective tissue; they all belong to the family of *connecting (supporting) substances;* all are derived from the primitive mesenchyme, and, from the standpoint of their evolution, they have equal importance.

One should not be surprised, therefore, to see bone revert to connective tissue, cartilage transformed directly into bone, or tendinous tissue become infiltrated with calcium salts and transformed into bone. In fact, tissues of the connective tissue group undergo ready and frequent transformations.

The concept of Reichert has been accepted by all biologists; it has stood the test of time; and today it represents only elementary knowledge. Nevertheless, it de-

serves our attention, because too many physicians consider bone as a specific tissue, a kind of histological entity. They forget its affiliation and that the idea of its connective tissue origin dominates all the problems of its growth and regeneration.

A. Osseous Metaplasia of Connective Tissue

Several details of the evolution of connective tissue seem necessary.

Connective tissue may present a series of evolutionary types which are variable in their degree of complexity and adaptation. Embryonic connective tissue is formed of numerous cells and a fundamental substance which is more or less abundant and contains very fine fibrillae (fibroglia, or threads). Under the influence of functional adaptations of its fundamental substance, adaptations which are peculiar and of a mechanism as yet little known, undifferentiated connective tissue may become specialized in some degree and assume various structural types; it may become loose connective tissue, a structure for filling spaces and to secure sliding movements; fibrous tissue with solid bands, powerful agents of resistance and traction; aponeurotic tissue, tendinous tissue, elastic tissue, etc.

Each of these evolutionary types may, in its own way, undergo a transformation of a quite different order. They can become impregnated with calcium salts, according to a complex mechanism which we shall study, and by reason of this assume a pronounced character of hardness and rigidity. When the tissue subjected to ossification is very young connective tissue, that is, unformed, there is produced a very hard, dense bone, which is the typical bone tissue.

If this occurs in a more highly differentiated connective tissue, a fibrous bone is formed, which is less hard and has other physical properties.

The functional value of the bone tissue obtained differs in its varieties, and these depend on the quality of connective tissue framework. Bone tissue has rightly been compared to reinforced concrete: the metallic framework is represented by the connecting fibrils; the cement is the calcified fundamental substance. It has likewise been compared to a plaster of Paris dressing, the gauze matrix assuring elasticity and solidity, the plaster the rigidity.

Bone which arises from embryonic tissue is always more dense and more resistant from the functional standpoint. Bone metaplasia occurring in fibro-aponeurotic tissue gives true, but membranous bone, such as is seen in the lower species (shells of fish); when produced in tendinous tissue it forms the long, hard, tapering needles of ossified tendons.

This general biological conception is particularly useful in comparative anatomy. In the fish group the varieties of connective tissue are innumerable: scales, spines, and different skeletal pieces. Stephan, in a series of researches on the bone tissue of fish, has developed this conception and has drawn from it important biological considerations.

If the connective tissue is in an embryonic state, either because of the youth of the animal or its situation in the body, the fundamental substance of the bone is but slightly differentiated, and the tissue as a whole has great mechanical value. If the ossification takes place in a fibrous region, already highly adapted, there is formed bone with coarse bands, which has little resistance. Little by little this law becomes clear: that the less differentiated the connective tissue matrix, the better the bone is physiologically. The more delicate the connective tissue framework, the greater becomes its mechanical value. *The physiological worth is inversely proportional to the histological differentiation.*

The precocity of ossification, preventing all later differentiation of the fundamental connective substance, represents, therefore, physiological perfection. It is a

tendency of the same nature as that leading to the early differentiation of organs in the course of embryological development. One might call this phenomenon *histogenetic acceleration.*

Bone is therefore a metaplasia, or rather a *metamorphosis,* of connective tissue.

This idea of bone metaplasia having its effect on connective tissue at varying stages of evolution is of capital importance for the understanding of the facts of the growth and repair of bone.

B. General Structure of Bone

Many misunderstandings arise from lack of precision in the terms employed. The names brought into use by the first histologists are still employed. They may have a precise meaning for professionals who are familiar with their tradition. But because of a series of changes from their original meanings, the actual value of these terms escapes the majority of physicians. Definitions are therefore indispensable.

The histological structure of bone is determined by its connective tissue matrix.

Embryonic connective tissue is one which is still undifferentiated; it contains an abundant fundamental substance, which consists of very delicate fibrillae. The fibrillae are not arranged in any given direction, but form a delicate network, and do not form bands. The cells, or fibroblasts, are large and possess a few prolongations which form anastomoses with neighboring cells. It is mesenchymatous tissue like that of the embryo, consequently it is adapted to all types of morphologic changes, and has a great, almost infinite possibility of growth.

Its richness in capillaries is extremely variable. It may contain a great many or, on the contrary, be almost devoid of them; in the latter case its nutrition takes place by diffusion.

All newly formed connective tissue first appears as embryonic connective tissue. For example: the tissue of repair or granulation tissue.

Fibrous tissue is a connective tissue in which the fibrils have become predominant. In it they are organized into bands. This is always a form of secondary adaptation. Already highly differentiated, fibrous tissue is less subject to metamorphosis, but may, however, undergo some changes. It is an adult tissue.

Embryonic connective tissue may be invaded by blood vascular elements which colonize it and transform it into

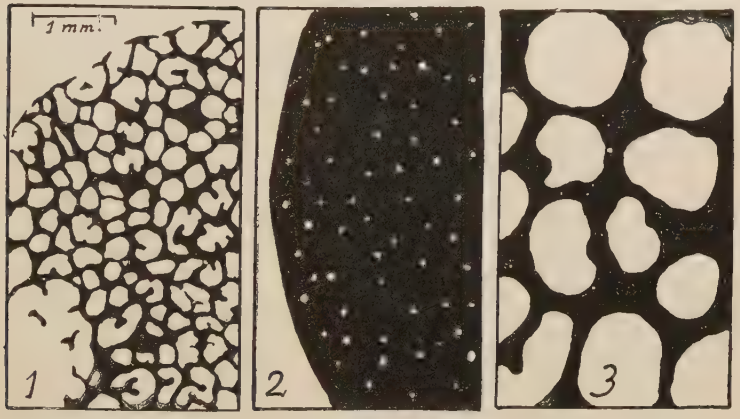

Fig. 1.—Relative richness of young bone in bone substance (*1*), of compact bone (*2*), and of spongy bone (*3*) in man.

hematopoietic tissue. This is what takes place in the bone marrow. Contrary to what is often thought, that which is given this name is not an element of bone. It is only a parasite. Under certain conditions, it may be separated from the bone. The connective tissue framework having become freed resumes all its original sharpness and its evolutionary possibilities.

The parts of bone which have not become ossified and which have remained reticular tissue are commonly called medullary spaces. This is an expression which may give

rise to confusion. One often confounds, under the name of marrow, the connective tissue space and its contents, the hematopoietic elements which are the result of colonization. For this reason, it would be better to use the expression, connective tissue spaces of bone. The employment of these terms with a double meaning has given rise to much confusion.

Representing calcified connective tissue, bone embraces the following elements:

(a) Fibrillae, the connective tissue fibrillae.

(b) Cells, the bone cells, elements having a very sluggish life.

(c) An intercalary substance (matrix). This is calcified and hard, and encloses fibrillae and cells.

The cells are lodged in cavities (lacunae) in the hard fundamental substance. The cells may disappear while the cavities remain.

Delicate anastomosing canaliculi unite these cavities. It is unlikely that all of these canaliculi contain cellular prolongations.

With this identical fundamental constitution, which is always present, bone represents diverse types of histological architecture. In man and the other mammals, in either normal or pathological states, there are three principal types: embryonic bone, spongy bone, and compact bone.

(a) *Embryonic bone* is made up of an assemblage of irregular delicate bars and lamellae of bone which form a small meshed network. One readily finds in it the framework of the original matrix. Generally bars and lamellae are arranged without order or in any particular direction: such tissue lacks fixed structure.

The connective tissue spaces are usually of embryonic type and the capillaries are relatively few in number. The fibers and connective tissue bands are directly continuous with those of the connective tissue matrix of the calcified lamellae.

Bone of this type is very unstable: it may easily disappear.

In speaking of it, the terms *young bone, imperfect bone,* or *coarsely fibrous bone,* are frequently used. It is important clearly to understand these common terms.

(b) *Spongy bone* has likewise an arrangement in bars and plates and interlamellar spaces. But here the framework is much thicker and the spaces are much larger than those of embryonic bone.

The bars and plates of spongy bone are formed by the grouping of several bone lamellae, and contain lacunae and bone cells.

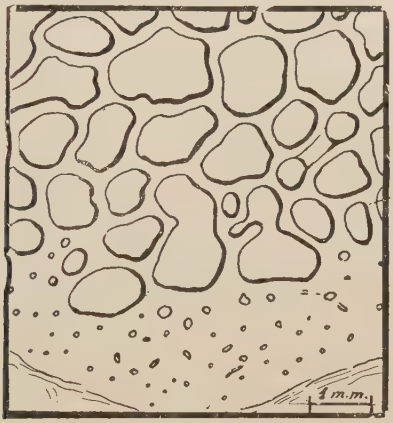

Fig. 2.—Diagram of a transverse section of an epiphysis, with a covering of compact tissue and spongy tissue.

Either the connective tissue in the spaces is transformed into fatty tissue or the spaces are secondarily filled by hematopoietic tissue.

(c) *Compact bone* has a framework which is very thick and is formed of a considerable number of lamellae. The connective tissue spaces in it are very small and do not contain hematopoietic elements. The lamellar systems representing the original framework are arranged around the canalicular connective tissue spaces, which contain a single blood capillary. All of these canals follow the same

direction and are parallel to the long axis of the diaphysis. The make-up of the tissue has for this reason a special architecture, first recognized in the eighteenth century by the English anatomist Havers. Since that time these canals have been known as Haversian systems and bone of this type as Haversian bone.

Recently, several histologists have tried to make the Haversian systems the structural units of bone, and have given them the name of *osteons*. This neologism is useless.

The physiological significance of the Haversian arrangement of compact bone is relatively unknown. By what series of adaptations to pressure and traction is this

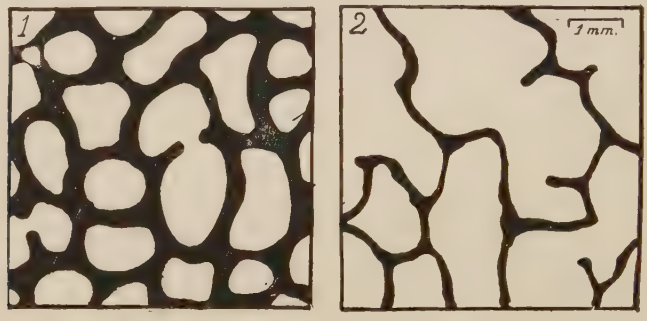

Fig. 3.—Varieties of spongy bone. Different thicknesses of their bone trabeculae.

peculiar architecture formed? We do not know. In spite of the classic character of this structure, it must not be forgotten that it still has many obscure points.

The number of lamellae to the square millimeter in Haversian bone is very great. In man it is about 800 (Welcker, Harting).

II. THE GENERAL COURSE OF OSSIFICATION

The formation of bone viewed in its broadest aspect (embryos, repair of pathological bone, comparative histology, etc.) seems at first glance to follow two very different courses.

In the first type bone always follows cartilaginous tissue. It is said that a cartilaginous form precedes it; and, for a long time it was believed that this transformation was direct, the fundamental cartilaginous substance becoming, through impregnation with calcium salts, the fundamental bone substance, and the cartilaginous cells becoming bone elements.

Johannes Müller (1836) showed that the process was in reality infinitely more complex. Cartilage does not become bone directly, but undergoes resorption and disappears in order that it may finally be replaced by bone. Bone is produced, not by transformation and metaplasia, but by substitution and neoplasia. The cartilage is progressively resorbed and is gradually replaced by embryonic connective tissue which becomes ossified. Ossification of cartilage is in reality only the ossification of a substituted connective tissue.

In a second type, which was unknown for a longer time, there is a direct transformation of connective tissue into bone without the intervention of cartilaginous antecedents. It is this type which has been described by Heinrich Müller, Virchow, Sharpey, Bruch, Kölliker, etc., but not, however, without contradiction.

In this second type the transformation is direct; the connective tissue becomes bone through metaplasia.

More recent works have demonstrated that it was necessary to add to the preceding a third method of osteogenesis. Without substitution and without previous destruction, cartilaginous tissue may become bone. This chondro-osseus metaplasia is infrequent in the normal evolution of the human organism. It is, however, observed more often in the course of pathological osteogenesis and in the bone development of the lower vertebrates.

It is to be noted that parallel with this metaplasia, and in its vicinity, phenomena of resorption are constantly to be observed: either resorption of a pre-existing cartilag-

inous tissue or of bone formed in previous stages. Resorption and ossification are placed in juxtaposition in manifold ways. Their combinations give rise to the very diverse types of osteogenesis and the complex pictures presented by tissues in the process of ossification.

We shall study especially the processes of direct ossification in connective tissue. These are the clearest and the most easily defined. It is through the study of these that progress will be most easily attained.

Ossification in cartilage is far more complex. The phenomena of cartilaginous resorption obscure the essential mechanism. This is probably one of the explanations of the slowness of our progress in this part of physiology. In spite of innumerable works and meritorious labor, the question has not advanced, because the experimenters have been hypnotized by research on the part played by cartilage. They have, in fact, chosen the poorer substance for study.

The problem of osteogenesis becomes clearer when one views it as an example of simple metaplasia of connective tissue. On the whole it would have been better for the development of our knowledge if the first histological research had, in the beginning, been applied to pathological ossifications. The processes of ossification in them are infinitely more simple than are those in normal organisms. This proves once more that very often pathology is a remarkable field for biological analysis.

Bone metaplasia in a connective tissue area presents in general three phases:

(a) The connective tissue becomes edematous and tends to revert to an embryonic state.

(b) In this prepared connective tissue there occurs an infiltration of a special nature (pre-osseus infiltration).

(c) This pre-osseus substance is impregnated with calcium salts and becomes hard. Bone is then formed.

There is obviously something artificial in the distinction of these three phases. It has only a didactic interest.

Life processes are not divided into a fixed number of compartments. But if one does not make the mistake of believing that these compartments are water-tight, the distinction is legitimate for it permits one to form a simple idea of a complex phenomenon.

For the sake of convenience one may name these phases. The first recognizes the creation of an ossifiable medium; the second is characterized by infiltration with pre-osseus substance; and the third by the deposition of calcareous material.

The expression "ossifiable medium" may at first sight surprise one. It means simply that histological modifications render the connective tissue liable to impregnation.

Our personal research has been made especially on adult man, on war wounded, for whom the processes of bone repair have been followed by repeated biopsies, the findings of which were supplemented by the regular clinical and radiographic examinations. Undertaken to determine the mechanism of bone repair in war fractures, our researches have led us to examine all the sections of bone pathology with which we could come in contact. It is therefore the osteogenesis of repair and pathological osteogenesis which have served as the objects of our study.

On the other hand, we have not examined the evolution of bone in the embryo. It is not at all paradoxical to think that the study of the embryological formation of bone gives us only mediocre and insufficient information in regard to the mechanism of osteogenesis. In the embryo these processes are superimposed on the complex series of growth phenomena.

In every question one should strive to attack first the best laid down and the clearest problems. It is probable that by studying ossification in connective tissue one will arrive more easily at the comprehension of the whole mechanism of osteogenesis.

CHAPTER II

THE CONNECTIVE TISSUE PHENOMENA PREPARATORY TO OSSIFICATION

In a connective tissue which is to become ossified, there are unfolded some modifications involving the interstitial substance and the cells. These transformations are the following:

I. Edematous infiltration;
II. Multiplication of the connecting fibrils;
III. Deposition of a pre-osseous substance.

With the study of these initial phases of osteogenesis there is connected the examination of two important problems:

I. The part played by the cells in the genesis of bone (study of the osteoblastic theory);
II. The possibility of cartilaginous evolution.

I. EDEMA

In a region soon to be ossified, the most important morphological fact is the appearance of an edematous state which is hard and lardaceous and peculiar to connective tissue. One can easily demonstrate this in the vicinity of a bone which has been fractured a few days previously. About the fourth or fifth day, all the connective tissues around the traumatic area, periosteum, marrow, and neighboring tissue spaces, are edematous and swollen. A substance, gelatinous rather than liquid, has infiltrated their interstices.

This is not an ordinary edema. It is an infiltration which is more colloidal in nature. Gerdy (1885) spoke of it

as less "a fluid and quivering lymph than a fibriniform red or pink substance." This lymph represents the bone "juice" of the old writers.

Although this swelling of the fundamental supporting substance preliminary to ossification has been observed for a long time, it has not attracted the attention of either physiologists or histologists.

Nowhere in modern works is it explicitly noted. The swollen character of the tissue at points of primitive ossification (Urlymphe of the mesenchyme) has been viewed only in its morphological aspect and not as a physiological state. Recklinghausen, however, seems to have had a vague idea of the importance of this process; for he gave slowing of the lymphatic current as a condition necessary for calcification.

One finds this edema only in localities where bone is going to be formed. When it is lacking at the site of a fracture, one should fear nonunion and the probability of a pseudarthrosis.

This edematous infiltration therefore merits attention as one of the fundamental elements of the process of ossification.

Histologically, the edema has no special character. The fluid impregnating the connective tissue medium is formless and has no particular staining qualities. Connective tissue thus infiltrated shows under the microscope the usual condition of edematous tissues: swelling of the fundamental substance, and separation of the fibrils and connecting bands. At bottom, the phenomenon is rather macroscopical than histological. This is a very clear example of changes, obvious to the naked eye, which disappear under the microscope, the more readily as the magnification is increased.

The infiltration is at times so extensive that one witnesses in certain conditions the formation of a true serous col-

lection. In unreduced fractures, at about the twenty-fifth day, we have found an abundant clear liquid in a kind of interfragmentary cavity. This is not a hematoma, for there is not found the slightest clot. This liquid represents, if not the infiltration itself, at least the exudation of one of its products of transformation collected in an interspace.

What is the nature of this infiltration? The only fact which appears to us approximately certain is that the infiltrating liquid is not exactly similar to an edematous transudate. But it remains necessary definitely to fix, by chemical research, this idea which has, up to the present, arisen only from impressions.

There is certainly fibrin in this exudate. It is possible that the fibrinous filaments may be the source of the connective tissue fibrils, the number of which increases considerably. This constitutes an histological problem into which we will not enter.

Chemical and physicochemical study of this substance remains to be done in its entirety. Research in this direction will probably be most fertile. In any event, this edematous infiltration appears to be the starting point of ossification: without it nothing is set in motion. Dry tissues do not ossify.

Does this edema arise from a slowing of the lymph, from stagnation of the interstitial fluids, or does it depend on local hyperemia? This point will be solved with difficulty. Zones which are soon to be ossified generally have few vessels. This edema appears to be linked with a defective circulation and with a stagnation of the fluid in the tissue spaces. This stagnation of the humours seems to be one of the necessary conditions for the formation of the bone trabeculae, but evidently does not necessarily evoke it. All ossification takes place in an edematous tissue, but it does not follow that the edema occurs *because* of the ossification.

It should be remarked that the newly formed spicules of bone are always situated as far as possible from the

blood capillaries which enter the nonossified connective tissue spaces. In their immediate neighborhood, where interstitial stagnation is least, there is never bone formation.

Another fact is seen in the examination of tissues which are ossifying. There is never any infiltration with polymorphonuclear neutrophilic leucocytes in connective tissue areas which are in the process of ossification. Bone formation never occurs in areas which are infiltrated with these elements. There appears to be a positive antagonism between these two processes. This inhibitory action of the polynuclear neutrophiles may probably be ascribed to their digestive properties.

In short, one can make clear but two conditions for the source of the connective tissue preparation: Interstitial stasis and the absence of neutrophilic diapedesis, both depending on the state of the circulation of the blood in the region considered. After all, it is the circulatory condition which determines this connective tissue preparation. It represents what has been called *irritation,* a poor term which should be abandoned.

These ideas allow us to understand why a slight infection seems to favor the development of new bone. It acts by increasing the interstitial stasis, which in consequence favors pre-osseous connective tissue transformation. But, if it is intense enough to provoke an infiltration with polynuclear neutrophiles, it will interfere with bone formation at such points. There will be formed only bone of a loose, areolar-like structure with large interspaces, bone which is physiologically inferior. If the infection is considerable, the neutrophilic infiltration is such that all new bone formation is impossible.

This offers a ready explanation of a very perplexing question in bone surgery: Why does infection sometimes favor and sometimes hinder bone regeneration?

II. MODIFICATIONS OF THE CONNECTIVE TISSUE NETWORK

Contemporaneous with the edematous infiltration of the connective tissue substance, one notes modifications of the fibrillary network. These are registered on the fibrils, while the connective tissue bundles or fibers, properly speaking, are generally unchanged; however, one notes at times that these latter are swollen and that there is a kind of separation of the framework which forms them. But these changes are relatively restrained. In a general way connective tissues of a fibrous type rarely ossify (true ossification) without first undergoing a return to the embryonic state.

The elastic fibers remain inert, without change. They play a passive rôle exclusively.

The method by which multiplication of elementary connective tissue fibrils occurs is one of the most complex and disputed problems of contemporary histology. The part played by the cells in their formation is particularly disputed. We will not enter into the questions to which it has given rise.

The multiplication seems, in most cases, to follow edematous infiltration. The increase in this network takes place in a fundamental substance which has become modified. It is not identical in all areas. In certain localities there are true arches formed by a close fibrillary network.

It has not seemed to us, at least from a general examination of the subject, that the cells play a part in the multiplication of the fibrils.

That augmentation of the connective tissue fibrillary network occurs preliminary to ossification has long been known. Spuler, von Korff, Mays, and A. Hartman, among others, have pointed it out, and have justly ascribed great importance to it, making of it the essential process in the origin of osteogenesis. It is so apparent with specific methods of staining that one cannot fail to see it. It is

among these fibrillary lines that the first deposit of pre-osseus substance appears.

Connective tissue fasciculi undergo changes of a quite commonplace order. They appear swollen and more sharply defined. They will eventually be enclosed in the new bone. They will become the fibers of Sharpey. These may sometimes be the center of formation of new ossified trabeculae. Around the connective tissue bundle a con-

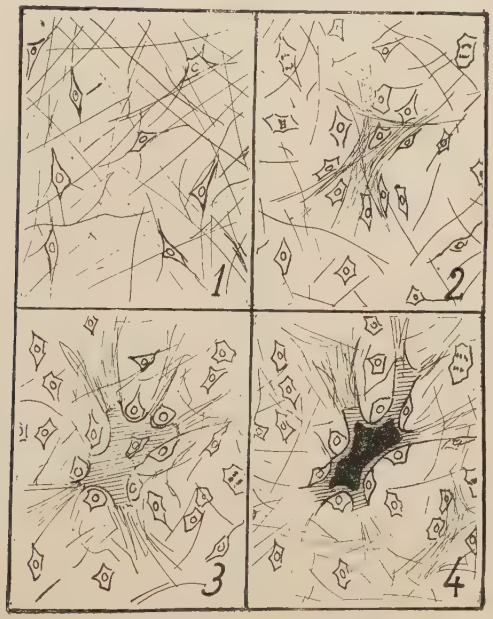

Fig. 4.—Diagram of the phases of ossification. *1*, Connective tissue edema. *2*, Multiplication of fibrils. *3*, Deposition of the pre-osseous substance. *4*, Deposition of calcium.

densation of fibrils takes place, a true network is formed and the pre-osseus substance is deposited in this. The whole is later calcified. The connective tissue fiber has become a fiber of Sharpey.

The intervention of fibrils in the formation of bone is of great physiological importance. The fibers give to bone its solidity and cohesion. The calcium salts supply rigidity.

The quantitative variation of the fibrils conditions the mechanical quality of the bone. As we shall see later, it is through their arrangement and their quantity that in the last analysis all of the processes of morphogenesis and adaptation of bone are brought about.

When knowledge of ossification is sufficiently advanced to enable one to state the problems involved in the formation of bone having such and such a mechanical quality, it will then be necessary to revert to this initial process of the multiplication of the fibrils and of the formation of the network, the essential framework of the columns of bone.

III. THE LAYING DOWN OF PRE-OSSEOUS SUBSTANCE

In the modified connective tissue in the network of connective tissue fibrils, there appears a homogeneous substance of special refractivity. From this moment the fibers of the network are clearly outlined.

This homogeneous substance is not hard, although viscous and resistant. It is uncalcified. It is pre-osseous substance, sometimes called osteoid tissue. The lines which it forms have the arrangement of the future bone trabeculae. Anatomically, it is really bone which is formed, soft bone, chemically not yet calcified, functionally not yet hard, but histologically fully characteristic. From the examination of a decalcified piece of bone, it is often difficult to know whether one is dealing with bone in process of formation or with fully formed bone.

Almost immediately after their appearance, the lines of the connective tissue latticework are infiltrated in their center with calcium salts which render them hard. The preosseus substance is nothing more than a hyaline margin of about 5-30 microns in width.

The bone spicules or trabeculae seem sometimes to appear suddenly in the infiltrated connective tissue. At other

times they seem to propagate themselves from pre-osseous trabeculae which have been previously formed and are already calcified. It is a kind of phenomenon which diffuses itself, a process which spreads gradually in the modified connective tissue.

The pre-osseous framework pushes out in every direction and may not take on any orderly arrangement. The whole then forms a spongy mass with regular trabeculae. At other times the trabeculae tend to follow the same general direction, and some arrange themselves in relation to the others like transverse anastomoses. Their direction is probably determined by divers factors the study of which constitutes bone morphogenesis.

There are in the first place mechanical factors. Traction tends to orient the trabeculae in the same direction as itself, that is, in the simpler case where the traction is always exercised in the same direction. When several forces play a part, the arrangement is determined by the components. The problem is then always very complex, for it is difficult to grasp the variable elements in play, and their combination. We shall return to them later.

Through these forces acting especially on the genesis of the fibrillary elements, one may, according to von Korff, readily explain the disposition of the columns of bone. But they do not operate alone. The vessels seem to play a part also.

As a general rule, deposits of pre-osseous substance occur at points removed as far as possible from the vessels. One may almost predict the direction of the bone columns when one knows the direction of the capillaries.

Finally, there is a third factor in the inhibitory action which the histological fasciculated elements (connective tissue fibers and muscle fibers) exert on the extension of the bone columns which touch them perpendicularly. Having reached the fasciculated bundles, the bone columns, or trabeculae, are bent in their direction and do not extend

beyond them. The column bends itself. Through this, in a way, these limiting fasciculae dam up the extension of bone and thus play a part in a great number of normal and pathological ossifications (the rôle of the periosteum, genesis of pseudarthrosis, etc.).

The conception of a pre-osseous substance differing from ordinary fundamental connective tissue substance and in which calcium deposit takes place is very old. It is due to Müller.

Since this author, numerous facts have proved the solid foundation of this idea. A kind of hyaline matrix capable of infiltration with calcium has been recognized, not only in the bone of vertebrates, but in a great number of hard calcified formations of lower animals. Recently Marcel Prenant has demonstrated that, among mollusks, it is the connective tissue cells which have undergone hyaline degeneration which become calcified cells; it is the intercellular hyaline collections which accumulate the calcium.

The chemical nature of this hyaline substance is still unknown. By a misuse of words it is sometimes called ossein. But the word ossein has a definite chemical meaning. The broad lines of its composition are known, while we are entirely ignorant of the nature of the pre-osseous substance. We have no right to consider it as ossein, even though it is very probable that it is made up of a substance belonging to the same group.

Its chemical basis seems to be collagen more or less condensed or modified. We know nothing of its physical character or of the causes of its refractivity and viscosity. Is it merely a phenomenon of colloidal condensation? This is a histochemical study which has yet to be made.

Among its physical properties, its very special refractivity merits notice. It is this which gives it its characteristic glossy appearance.

Its very great viscosity renders it solid, although not hard. Like the fundamental cartilaginous substance, it

is too thick to permit leucocytic passageway and the ingrowth of newly formed vascular tissue.

Pre-osseous substance appears to possess a very great tenacity and elasticity. One never sees it either broken or fractured, a thing which, on the contrary, is frequent in true bone substance.

Fig. 5.—Deposition of the pre-osseous substance. Precise arrangement of the deposit in relation to the cells. It is seen how the pre-osseous substance follows the fibrillary bundles, slipping between the hypertrophied or degenerating cells (osteoblasts).

Pre-osseous substance closely resembles infiltrating materials such as hyaline, intracellular cement substance (Kittsubstanz), amyloid and the basic material of cartilage. These resemblances are above all of a morphological and

physical order. We know too little of the chemistry of these bodies to go beyond these rather coarse analogies, but they should nevertheless be kept in mind. One of the common characteristics of all these substances is their propensity, more or less great, to fix calcium salts in a colloidal form.

All the modifications of which we have just spoken: edema, multiplication of fibrils, pre-osseus condensation, appear to depend on variations of the circulatory system. Without them these changes are not produced. When they take place, the circulation is always modified. In short, the creation of an ossifiable medium and pre-osseous condensation seems to be but the consequence of circulatory changes.

IV. THE PART OF THE CELLS. THE THEORY OF THE OSTEOBLASTS

In the course of the initial processes of osteogenesis, while the faint form of the bone framework is being established, the elements of the connective tissue of the region in process of ossification do not remain inert. They show changes which it is the more necessary to specify since classical histological theories still dominate our conception of osteogenesis.

It is not our intention to give a complete exposition of this question. The number of works published on this subject is considerable. The detailed abstracting of all of these documents and of all these theories, however interesting it might be, is obviously beyond the scope of this book. Conforming to the general plan of this work, we will confine ourselves to delineating the larger aspects of the question.

A. Initial Modifications of Connective Tissue Cells

In a region which is being ossified, the connective tissue cells undergo important modifications. The most notable

consist of their swelling and hypertrophy. While preserving their general morphological character (protoplasmic processes, form, etc.) they become more voluminous. Their activity appears to augment. They show numerous mitoses. While in this state they are called osteoblasts.*

Mitoses are seen only in a very limited zone, at a certain distance from the margins of the bone trabeculae in process of formation. They are not encountered in the regions where, strictly speaking, there are unfolded the phases of ossification. When the cell has taken on the characteristics of an osteoblast, it ceases to multiply by karyokinesis.

Following their increase in length, the cells never show cytological signs of secretion.†

These cellular transformations are never produced prior to edematous infiltration, but at the same time with it or afterwards. They are visible only at points modified by edema. Cellular change, being subsequent to the edema, appears to be dependent upon it. On the other hand, one cannot attribute the processes of connective tissue edema to any cellular secretion whatsoever.

This point is most important. Below, in the study given to the osteoblasts, we shall see that the whole process of osteogenesis has been attributed to these cells. The facts noted here tend to contradict this idea, since the formation of the osteoblasts is secondary to edematous infiltration.

B. **The Theory of the Osteoblast**

Although it has been recognized for a long time, the preosseous substance has been considered as a product of

*The modifications described above are characteristic of fibroblasts and occur in the fixed connective tissue cells in any area in which active hyperplasia of the connective tissue is taking place. The chief difference between osteoblasts and ordinary fibroblasts is that the osteoblasts stain more deeply with the basic dyes and they are often located at points where new bone is obviously being formed.—*J. A. K.*

†The fact that the osteoblasts show no cytological signs of secretion is no proof that they do not pour out some substance which has to do with the fixing of calcium. Fibroblasts show no signs of secretion, yet many observers believe that the collagenic fibers are the product of these cells. In some glandular and epithelial cells we have definite evidence of a secretion, but the precursors of this secretion have not yet been identified.—*J. A. K.*

cellular secretion. On the one hand, in connective tissue which is ossifying there are voluminous connective tissue cells, and, on the other, our nature has an unconquerable tendency to attribute to a cellular secretion most of the deposits observed in tissues. The cellular theory, a fundamental conception, has somewhat tyrannized the histologists. They have always been reluctant to admit that certain anatomical forms are only physicochemical transformations of interstitial media brought about without cellular intervention.

Also one should thoroughly comprehend the classical theory of Heinrich Müller, who saw in the pre-osseous substance the effects of the peculiar activity of the swollen and hypertrophied cells which are seen in connective tissue in course of ossification. Waldeyer, Gegenbaur, von Ebner, etc., have ranged themselves on the side of this conception.

But if, on their authority, the part of the osteoblast has become true dogma, then there should be agreement as to the mechanism of its action.

The following opinions have been held.

According to Gegenbaur, the osteoblast secretes bone substance in the same manner in which a glandular cell pours forth its secretion.

For Waldeyer, the osteoblast degenerates and in dying incorporates itself in the fundamental connective tissue substance, thus transforming it into pre-osseous substance. The true bone cells are undegenerated connective tissue cells, inclosed in the pre-osseous substance; these are not osteoblasts.

In the view of Studnicka, Retterer, A. Hartmann, etc., degeneration affects only the peripheral portion of the osteoblast. The center (nucleus and endoplasm) lives and becomes the bone cell.

In the classical conception of Gegenbaur, the connective tissue cell becomes an osteoblast, secretes pre-osseous ma-

terial, from either one or all of its aspects simultaneously; in this case it is as if the cell became imprisoned in its secretory product. The anastomotic union of the cell with the neighboring elements does not disappear. The osteoblast remains in the community of connective tissue cells.

Fig. 6.—New bone 17 days old in active growth in juxtaperiosteal tissue. There are no osteoblasts at the point of increase of the pre-osseous substance.

Osteoblasts have two morphological appearances; either they are hemmed in with pre-osseous substance and thus transformed into bone cells, or they remain side by side in the manner of epithelial cells. It has been believed that

in this epitheloid disposition there is seen proof of the part played by these elements in the genesis of bone. They are met with only where bone growth is active, that is, where the pre-osseous substance is being laid down. On the other hand, at the points where there is no bone generation, these osteoblasts are lacking. Nothing more than elements of the fibroblastic type will be found here.

In the view of the majority of authors, osteoblasts are connective tissue elements of some sort, which have acquired by an indefinite mechanism the capacity to secrete bone substance. According to others, they are strictly specific elements, the essential property of which is to secrete bone. Among these specific elements, even, there exist varieties, a kind of hereditary specialization of a common type (Macewen). These specific elements are found only in the periosteum and epiphyseal cartilage. Kinds of osteogonies (osteogenic cells), they would be liable to displacement and transport by the blood stream. Thus is easily explained the formation of heterotopic bone.

It seems useless to us to elaborate on this fanciful view which eludes all discussion.*

C. Critical Consideration of the Theory of the Osteoblast

The classical theory has not lacked opponents.

Von Korff, and with variation in detail, Mummery, Spuler, Hansen, Nageotte, etc., think that osteoblasts have nothing to do with the formation of pre-osseous material. This formation is an exclusively interstitial phenomenon. We have supported this conception since 1918, after having tried in vain to explain such a highly specialized function in these cells.

A single histological fact allows us at once to ask a pre-

*The osteoblastic theory does not require a specific cell which must needs be transported from one location to another in order that new bone may be formed, but simply assumes that certain cells, namely, osteoblasts, have something to do with the laying down of bone. Under certain conditions which are as yet poorly defined these osteoblasts may be created *in situ* by a metaplasia of the fixed connective tissue cells.—*J. A. K.*

liminary question: If the osteoblasts truly secrete pre-osseous material, why does one not encounter among them cytological evidence of a secretion? However, no method has shown certain evidence of secretory antecedents in these cells. But there are additional objections.*

One of the essential points of the classical theory is found in the absolute coincidence of the osteoblastic deposits with formation of new bone, and vice versa. Now, the formation of pre-osseous substance has been often observed without the presence of osteoblasts. We have personally noted the absence of osteoblastic deposits in foci of new bone formation, the existence of which was established by macroscopic and radiographic observations. And conversely, at points where there was no osteogenesis, but on the contrary, arrest and limitation of bone, we have observed rows of osteoblasts of an epitheloid type. Likewise, Ely has cited cases in which, radiography and examination showing a resorption of bone, there were present typical osteoblasts limiting the trabeculae. Here, the disposition of the osteoblasts corresponded exactly to a limitation of the bone.†

In short, there is no coincidence between osteogenesis and the presence of osteoblasts.

Elsewhere, there are in normal development, zones of bone growth in which there are no cells, such as the bone

*See note on page 39.

†In my experience areas of new bone formation have contained large numbers of the cells which we call osteoblasts. These cells were intimately associated with the deposits of calcium and many of them were obviously being enclosed by the newly formed bone matrix. It is true that in areas of new bone formation one side of the young lamellae may be devoid of osteoblasts, but this is usually the side away from that in which the bone is growing, while the other side of the matrix is usually covered with osteoblasts. It is true that in bone which is undergoing resorption the lamellae are often covered by osteoblasts. This may be interpreted as evidence that the osteoblasts can reverse its function and not only can influence the formation of bone, but can influence its absorption. Other than increase in size and multiplication of the nuclei, there is no line of demarcation between osteoclast and the osteoblast. On the other hand, it may be that in atrophic bone the osteoblasts play a purely passive rôle, and it is not necessary to assume that they should disappear as soon as the process of new bone formation ceases and resorption commences. Of the two views I believe that the cells which we call osteoblasts may have to do with either the laying down of new bone or the absorption of existing bone, their function depending upon the physiological requirements in the given area.—*J. A. K.*

sheath enclosing the dorsal cord in the lower vertebrates. Bone therefore is independent of osteoblasts.

Let us add further, that in bone in process of resorption one notes the presence of multinucleated elements, osteoclasts, which arise from the development or fusion of osteoblasts. One accepts with difficulty the fact that an alleged specific element thus exercises two absolutely opposed functions.

In the lower animals bone cells play an evident part in the resorption of bone substance. Their return to a greater activity, characterized histologically by reversion to the osteoblastic type, coincides physiologically with osteolysis, that is to say, with the opposite of osteogenesis.

D. Mechanism of the Appearance of the Pre-Osseous Substance

How, then, is the formation of pre-osseous substance to be explained? In certain zones, quite distant from the blood capillaries, a transformation takes place in the fundamental connective tissue substance. Is this a transformation of the latter, or is some new substance added? The two mechanisms are possible and may be combined.

One has the impression that the transformation arises from a physicochemical modification of the connective tissue substance and of the interstitial lymph which it takes up. It results from a humoral process, a sort of thickening and coagulation on the spot, with or without chemical modifications of the collagen. The only cellular action which is admissible in the course of these changes is an indirect one, perhaps following the conception of Nageotte, by means of the secretion of diastases which act upon the fundamental substance.

These modifications seem reversible. In the course of bone resorption one may see the effacement of the usual aspects of pre-osseous substance and the reappearance of the fundamental connective tissue framework.

In the course of this transformation the connective tissue fibrils seem to disappear by effacement in the pre-osseous substance, the index of refraction of which is approximately identical. But one can rediscover them by unmasking them through suitable technic.

Fig. 7.—Invasion of the fundamental connective tissue substance by pre-osseous transformation.

E. Cellular Destruction and Its Rôle in the Genesis of the Pre-Osseous Substance

In the course of pre-osseous transformation, the osteoblasts immersed in the new substance become bone cells without much change of form. The most important modifications take place after the deposit of calcium salts.

A certain number of cells degenerate and disappear. There are fewer bone cells than there were osteoblasts. Generally they disappear quite unobtrusively through a kind of progressive effacement, without very apparent morphological phenomena. Nevertheless, one can see vacuoles and basophilic particles in some of the cells. These are not signs of secretion, but are signs of degeneration. Their presence gives rise to those views which explain the

origin of pre-osseous substance by partial and total degeneration of the cell.

In his researches on the repair of fractures, Fujinami advances an interesting mixed opinion. According to his theory, pre-osseous substance would probably be quite a simple intercellular deposit, formed without participation of the cells, which remain separated from it by a clear space. Subsequently the intercellular pre-osseous substance would be thickened by the introduction of materials derived from a part of the cellular protoplasm.

One sees that, in all these views, there is a common point, the combination of the products of destruction of cellular protoplasm with collagen, a combination which forms pre-osseous substance.

It is very possible that in dying, the cells liberate substances or ferments which impregnate the surrounding medium and more or less influence its subsequent behavior.

There is no isolated phenomenon in tissues. The death of an element reacts upon the functioning of its neighbors or upon the character of the surrounding medium. This common law must be applied to bone as to all tissues.

It is necessary to note, however, the disproportion which exists between the volume of the substance of the bone framework and that of the cells which degenerate. If the destruction of the cells plays a part in the formation of pre-osseous substance, it is perhaps by suppressing the very action of the cells and of their catalytic agents rather than by adding anything to the medium. In thus causing a rupture of normal equilibrium between cells and intercellular medium, this degeneration produces transformation in the interstitial medium.

F. **Meaning of Osteoblasts**

If the formation of pre-osseous substance is comparable to a noncellular local transformation of fundamental col-

lagen, what then is the meaning of those very characteristic transformations of connective tissue cells?

This point has been laid aside by the authors, who very justly have not accepted the secretory rôle of the osteoblasts. Denying them any rôle, they have not explained their presence, which is nevertheless indisputable.

We have thought that the osteoblasts might perhaps present reactionary forms of the connective tissue cells in the presence of the modifications of the connective tissue medium in which they live. The transformation of the connective tissue cells into osteoblasts would be the result of a change of medium.

The observed facts have seemed to verify the correctness of our hypothesis. There is a very exact equilibrium between the connective tissue cell and its medium. When the connective tissue medium is impregnated with cartilaginous substance, it is known that the cell becomes round, is enclosed in a capsule, and assumes the type of a cartilaginous cell. Thus, when the connective tissue medium undergoes pre-osseous transformation, there is modification and adaptation of the cell. To use a language clear but deplorably anthropomorphic, the cell seems to struggle against the transformation and thickening of the medium in which it lives. It tends to oppose it. As the connective tissue cells and phagocytic elements tend to become enlarged and to accumulate around a foreign body in order to dissolve it, so these cells, in the midst of a transformation which invades their medium, undergo an hypertrophy which leads to the formation of osteoblasts, and are grouped at certain points, which leads to the formation of osteoblastic deposits. Their enlargement (hypertrophy) may end in the formation of elements with many nuclei, the osteoclasts, the dissolving power of which, which is then maximal, becomes evident. Osteoblasts are therefore osteolytic elements also, but with weak powers, although their action cannot be verified histologically. The appear-

ance of osteoblastic deposits expresses, in short, reactionary attempts of the cells against the pre-osseous transformation which congeals their medium.

For the rest, bone cells, at least in young bone, and the osteoblasts, have phagocytic properties (Dubreuil, Bast). This last author, through ingenious experiments (the injection of Chinese ink in the growing parietal bone of new-

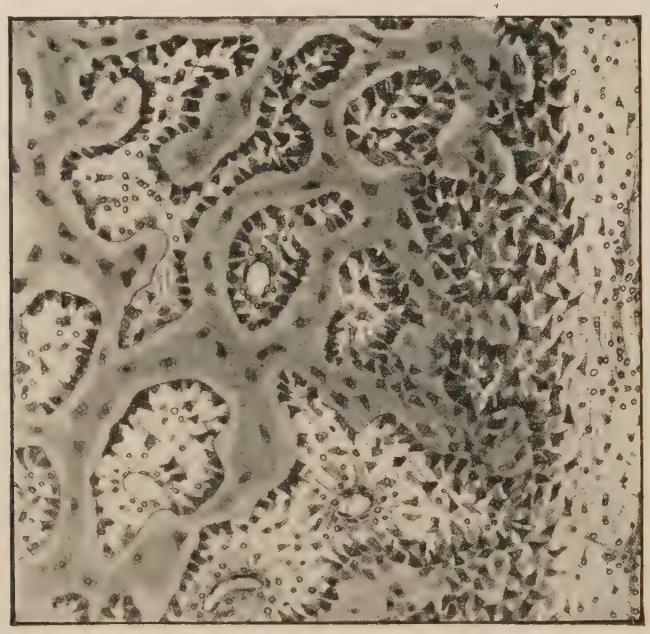

Fig. 8.—Limiting zone of bone growth. Hypertrophic osteoblastic deposits.

born animals) has shown that the osteoblasts were capable of phagocytic action on the granules of carbon. This suggests that the importance of the osteoblastic deposits may be the function of the number of connective tissue cells in the medium and not of the activity of the growing bone. Our observations on this point are very clear. When there is formation of new bone in granulation tissue which is very rich in cells, and even when the growth of bone is arrested, one may observe extraordinary osteoblastic de-

posits. Sometimes their development is such that one might believe that one was dealing with sarcomatous tissue. Thus in certain muscular osteomas which clinical and radiographic observations show to be absolutely arrested from the point of view of growth, if not in retrogression, the osteoblastic deposits are of extreme extent. But if, in the course of the formation of bone, the osteoblast on the whole plays such a secondary part, one may ask what in the fully grown bone may be the function of the bone cell which is derived from it.

If there is any at all, it is doubtless very slight. Bone is a tissue with a sluggish life. Physiologically, dead bone, with dead cells, seems to have the same mechanical value as when it is living. But as long as it is tolerated and as long as it is maintained in the organism, it seems to play the same mechanical part. Liesegang has very justly said that the bone cell is nothing but a useful parasite of bone. But as soon as it begins to resume activity, bone tends to disappear. One may think that like every fibroblast, the bone cell and the osteoblast tend to liquefy the collagenic substance which surrounds them and which, itself, tends spontaneously to thicken. There is a kind of antagonism between the interstitial medium and the cell, the latter tending always to liquefy the medium and to cause the collagenic substance to pass from a solid to a liquid state.

When the cell dies, which is the case with a number of elements at the moment of pre-osseous transformation, there is no longer anything to oppose the thickening of the interstitial medium. In our opinion the pre-osseous transformation represents this thickening, the fundamental process of ossification. The few cells that remain lose all activity. These are the bone cells.

One may then go further than Leisegang and affirm that the cell is injurious to bone, since, on resuming activity, this cell may cause a retrogression of the bone. The absence of living bone cells would therefore be a kind of

guarantee, an assurance, of bone tissue. But one must speak conditionally: other factors intervene, which modify the situation. We shall study them later.

It is seen that on the whole the formation of bone trabeculae is reduced to a very simple phenomenon. In consequence of a circulatory change (pre-osseous edema), the interstitital substance undergoes two modifications: the fibrils increase, so that their network becomes more compact; and the interfibrillary substance tends to thicken, and when its viscosity attains a certain degree, this substance presents a peculiar aspect which is characteristic of pre-osseous substance.

The connective tissue cells react against this thickening, by becoming enlarged and assuming the form of osteoblasts. It is a particular case of a great general law of connective tissue: the cell tends to liquefy the collagenous medium in which it lives, a medium which, in its turn, always tends to thicken. The osteoblast is only a commonplace reactionary form of the fibroblast.

But hypertrophic activity approximates degeneration. A great number of osteoblasts die. There is no longer anything to check the thickening of the medium. The pre-osseous framework is formed. This is the essential point of osteogenesis. As we shall see presently, the calcium deposit represents a commonplace biological phenomenon.

We do not conceal from ourselves the fact that this view runs counter to many classical ideas. It alone affords a full understanding of the facts of normal and pathological ossification. We give it today after long reflection and observations. If the criticism which it arouses permits the acquisition of new facts and new ideas, we shall think that we have not brought it forward in vain.

CHAPTER III

CALCAREOUS HARDENING OF PRE-OSSEOUS SUBSTANCE

When pre-osseous substance appears, its impregnation with calcium salts rapidly follows.

Histologically, bone is determined, in its specific form, at the moment the pre-osseous substance is deposited. The calcification causes no morphologic change, but produces profound modification from a functional point of view. The appearance of rigidity, a characteristic of bone and essential for its physiology, is due in particular to calcareous impregnation.

Calcification follows very closely the formation of pre-osseous substance. The uncalcified state is only a transitory stage. It is revealed in only a very small area, for as soon as it appears it is immediately impregnated with calcium salts.

On account of its biological importance, it is important to study closely this process of calcification, considering in succession the following points: the physicochemical condition of calcification, the physiological conditions, the rôle of the cells.

I. PHYSICOCHEMICAL BASIS OF CALCIFICATION

Before studying the mechanism of the deposit of calcareous material, it is advisable to explain the nature of this deposit. What is the hard calcareous material that is laid down in pre-osseous substance? And how is it laid down? This is the problem of the chemical nature and the physical state of the inorganic substances found in bone.

A. Chemical Nature and Physical State of the Calcareous Material in Bone

The calcareous material in bone is formed essentially of phosphate and carbonate of calcium. In young bone the most important element is phosphate of lime. Milne Edwards has pointed out that the younger the individual, the less abundant the calcium carbonate. Hugounencq has shown that, in the embryo, the phosphate greatly exceeds the other calcium salts, especially the carbonate. In the human species, the latter appears only in the second half of gestation. In the study of the first stages of osteogenesis, one ought to consider especially the deposit of calcium phosphate. But, in the adult the carbonate seems predominant.* There is little information, however, in regard to the chemical composition of newly formed bone in the adult.

One must think that in newly formed bone, even young bone developed in old individuals, calcium phosphate is predominant; the deposit of calcium carbonates is a slow, progressive phenomenon. It is important to keep in mind the idea of the constant physicochemical alteration of the mineral matter of bone. Under different influences, as yet practically unknown, slow modifications take place in the calcareous deposit: crystallizations, colloidal transformations, etc. It is a question, however, of a very general process. Recently Marcel Prenant studied alterations of the same type in the calcareous deposit of the epiphragm of the snail. The later carbonization of deposits, formed of tricalcium phosphate, seems to be quite a general

*According to Carnot (Compt. Rend. 156) the composition of bone (presumably adult) is as follows:

	Man			
	Femur (body)	Femur (head)	Ox Femur	Elephant Femur
Calcium phosphate	874.5	878.7	857.2	900.3
Magnesium phosphate	15.7	17.5	15.3	19.6
Calcium fluoride	3.5	3.7	4.5	5.7
Calcium chloride	2.3	3.0	3.0	2.0
Calcium carbonate	101.8	92.3	119.6	72.7
Iron oxide	1.0	1.3	1.3	1.5

—*J. A. K.*

phenomenon in nature. One finds it typically also in the formation of the shell of the snail. In the spring, the animal, through the medium of its phosphorous-laden mucus, secreted by its pedal organ, eliminates the calcium amassed during the winter. The mucus of the foot saturated with phosphate of lime and deposited on the edge of the shell is dried; the calcium salt is deposited secondarily, and carbonates are formed on exposure to the air, just as happens in mortars. The shell, formed first of calcium phosphate, later contains carbonate.

These differences of chemical composition explain the different staining of young bone tissue and that which is older.

The work of Basset has shown that chemically the calcified material of bone resembles the natural apatite (tricalcium phosphate with fluoride and chloride of calcium).

It is a composition more basic than tricalcium phosphate. It is found in this form in serum. In bone, it is mixed with a little calcium carbonate and traces of Mg, Na, and K, fixed by adsorption.

The processes of adsorption are very well marked in bone. In addition to the above elements, bone, especially if young, may take up iron, coloring matter such as madder, hematoporphyrin, etc., and can fix a whole series of metals. In the fossilization of bone, fixation of fluorin, iron, and even copper has been observed. All of these elements have been derived from the surrounding medium and slowly adsorbed in the course of centuries.

Either living or dead bone fixes foreign materials in approximately the same way.

The calcareous components are deposited in the bone matrix in a special physical form. W. Gerhardt affirmed that calcium salts in bone are in a state of colloidal deposition. In cartilage (calcified cartilage) they would be, on the contrary, in a crystalline state. Between calcification and ossification there would be an essential difference,

due especially to the physical state of the calcareous material.

The idea advanced by Gerhardt is very important; it is certain that calcified tissues (cartilage, for example) show histologically basophilic granulations, while the fundamental bone matrix in the same condition appears entirely homogeneous. Calcareous deposition of the crystalline type (calcified tissues) is therefore different from calcareous deposition of the colloidal type (ossified tissues).

Nevertheless, it would be erroneous to believe that the difference between these two extremes is absolute. Between a granular collection and one in amorphous form there is but a difference of size, and one must imagine intermediary types. From a certain size, probably at a very definite point, the physical characteristics of the deposit change. Instead of being opaque and refracting light strongly, the deposit is transparent and homogeneous like bone tissue. But as yet these physical studies are but little advanced.

B. Physicochemical Conditions of Calcareous Deposit

The problem under consideration is composed of two parts: first, the determination of the chemical nature of the materials in solution, the precipitation or solution of which leads to calcareous hardening; second, the study of the physicochemical conditions of their precipitation.

At first it was believed that calcareous impregnation was brought about by the dissociation of a soluble complex calcium phosphocarbonate existing in tissues in process of ossification. McKim Marriott has made a chemical model of this phenomenon by creating a clear complex calcareous solution, in such perfect equilibrium that, under the influence of variation in the quantity of one of its elements, it was precipitated. Several years before, Barillé had thought that tricalcium carbonophosphate, a salt of great instability, was found in solution in fluids in the areas in process of calcification. The breaking up of this tricalcium

phosphate probably set free the constitutents of bone tissue which were immediately precipitated.

It is probably this way. We have to do with substances in part dissociated into ions. At a given point, there are present: a calcium carbonophosphate in solution, ions of Ca, PO^4, etc., free, and solid calcium phosphocarbonate.

From the chemical point of view one can translate ossification into the following form:

$$\underset{\text{(ionized)}}{\text{Ca PO}^4} \longrightarrow \underset{\text{(dissolved and non-ionized)}}{\text{Ca}^3\ (\text{PO}^4)_2} \longrightarrow \underset{\text{(solid)}}{\text{Ca}^3\ (\text{PO}^4)_2}$$

This is the formula of ossification.

We do not yet know the nature of the complex and soluble calcareous mixture which precedes the appearance of hard bone. One suspects indeed that it especially contains phosphates, lime, and carbonates. But in what chemical form? From the nature of these phosphocarbonates in the blood it is impossible to draw conclusions as to their nature in the interstitial fluids.*

Into the phenomenon of calcification there has been introduced the idea of a "setting" of the calcareous substance, analogous to that of cement. The pre-osseous substance, while remaining soft, would first be impregnated with lime salts. A sudden transformation would take place in the colloidal state of the whole, which would then become hard. It is this "setting" which renders the connective tissue hard and gives it the characteristics of bone. This conception has been upheld by MacCordick in attempting to explain the calcification of arteries. The calcareous material would be deposited in soft masses in the walls of the arteries. Through the accumulation of CO_2 after death, or as a result of nutritive disturbance, it would become hard as a consequence of a true carbonation.

*According to various authors, from 55 to 75 per cent of the calcium in the blood serum can be removed by dialysis. The remainder is believed to be held by the proteins of the plasma.—*J. A. K.*

This brings out an hypothesis which requires verification. But one may remember that perhaps it is not necessary strictly to superimpose the biochemical process of calcareous deposit upon the physical process of hardening. The two phenomena are different and are not necessarily simultaneous; they may be consecutive. It is certain that in a connective tissue, one in process of ossification, the change from the soft to the hard state is sudden and without the intervention of intermediary stages. This sudden hardening is in favor of a phenomenon of "setting."

The second part of the problem consists of determination of the causes of the rupture of equilibrium.

In this balance, a great number of factors are at play: concentration of the Ca and PO_4 ions; solubility according to the medium of calcium phosphate; the P_H value; the part of CO_2 in solution; the intervention of chemical elements, of protein, for example, which may fix the Ca or phosphorus, etc.

Numerous chemists have studied this equilibrium and the mechanism of the deposit of solid calcium phosphates. Their works are important, but quite contradictory. Our incompetence in the chemical field does not permit us to discuss their results. We believe, however, that a fundamental reproach may be addressed to all because of their disregard of certain histological processes.

The Part of the Calcium and Phosphorus Content.—The work of American biochemists on rickets has brought out extremely valuable facts on this point. McCollum has shown that the absolute quantities of Ca and P in the diet and the proportions between these elements exercise a profound influence on bone growth. Every diet deficient in Ca, but with a relatively high content of P (or vice versa), leads to disturbance of bone development.

What the chemists have especially envisaged are the relations between the formation of bone on the one hand and the Ca and PO_4 content of the blood on the other.

These are the two extremes of the process, but in reality the precipitation of the calcareous material depends much less on the composition of the blood than on that of the interstitial lymph in actual contact with the pre-osseous framework. A material may be little abundant in the blood and very abundant in the lymph. The fundamental law of blood is the maintenance of the constancy of its composition. Owing to a series of mechanisms, blood throws into the tissue lymph excess material. The composition of the blood gives only a very incomplete picture of the intercellular fluids. It is the latter, however, that need to be known.

When the subject is considered from the standpoint of histophysiology, the importance of local processes in ossification is definitely proved to us. It is especially in the vicinity of regions which are being ossified that one should seek the variation of the calcium phosphorus content. One would probably find there a local excess of calcium, explaining the transfer, over a short distance, of calcareous elements liberated for bone resorption.

This idea, strictly histological and in consequence lacking chemical precision, permits the comprehension of the contradictory nature of chemical research. The richness of the blood in Ca and in PO_4 gives only a very imperfect idea of the richness of the interstitial lymph in these materials. What needs to be known is the composition of the fluids in exact contact with the connective tissue framework which is in process of ossification, an objective obviously difficult to attain.

Areas in process of ossification are in reality regions with a sluggish circulation, with difficult interchange. The composition of the blood in the great vessels permits no deduction concerning the chemical behavior in these areas. That is the weak point of all chemical research up to the present time. The methods are most exact, but that is not true of the object subjected to research. The problem on the whole

is badly put. And when well put, the methods are no longer applicable.

Understand us well. We do not intend to deny the very great importance of the researches of the chemists. But the very valuable information they give us is concerned only with the extreme phases of the phenomenon. What should be known is the richness of the interstitial lymph in areas undergoing calcification.

One may hope to have definite facts on these points only with the development of micro-chemical methods, which will permit us to recognize the composition of the interstitial fluids in the exact regions in process of ossification. Up to the present we lack this information.

The precipitation of calcium phosphate may be connected with increased concentration of one or both the ions of Ca and PO_4. Clarke has studied especially the increase of the Ca ion, Robison that of the PO^4 ion. The part of the phosphate ion seems the more important. The works on rickets have proved its preeminence. However abundant the Ca ion may be in the blood and in the food, it cannot be fixed on bone except with the aid of the phosphate ion.

Increase of the PO_4 concentration may be realized in two ways: by increase of the total inorganic phosphate, for example, following the hypothesis of Robison, by diastatic splitting of complex hexo-phosphates, or it may be through augmentation of the acidity of the medium (lowering of the hydrogen-ion concentration) leading to an augmentation of the PO_4 ion at the expense of the ions of PO_4H.

It must be admitted that all these ideas are still quite vague. They mark, nevertheless, sensible progress toward the physicochemical understanding of the problem. The latter of the two theories mentioned in the preceding paragraph is stated more clearly. On the disposition of

phosphate, a certain number of influences make themselves felt.

The Part of the Hydrogen-Ion Concentration.—It has been thought that one of the factors dominating the deposit, or inversely the absorption, of bone tissue, resided in the alkalinity, more or less great, of the local interstitial lymph.

This idea is very old. It has been rejuvenated since the hydrogen-ion reaction of the medium has been explained. It seems quite admissible and exact.

The consideration of the hydrogen-ion concentration may be interesting in explaining the characteristics of the solubility of calcium phosphate. But when one attempts to reconcile chemical results obtained in vitro with observations in vivo, biological impossibilities are often encountered. One should consider the variations of P_H (up to P_H 12 of Robison) which are absolutely incompatible with biological conditions. It suffices to recall that a normal solution of sodium hydroxide has a P_H of 14. That the P_H plays a part, and an important part, there is not the least doubt. But it clearly appears that this factor is not the only one. According to Freudenberg and Gyorgy, it would even be quite a minor factor because of its slight variations, as it is well known that all variations of little extent are prevented by a buffer mechanism which is put into play.

A series of recent works of Rabl, of Blum, and of their collaborators, on the influence of acidosis and alkalosis on bone tissue is related to this question of the rôle of the P_H.

Among the invertebrates (mollusks), calcium deposit is produced only in hyaline forms with an alkaline reaction. There is a certain relationship between the alkaline reaction of the matrix and the deposit of calcium.

The Rôle of Carbonic Acid.—For many years carbonic acid was thought to be of considerable importance. Hof-

meister thought that on account of it the calcium was held in the humors in a soluble form. As a matter of fact, the part played by the CO_2, without being denied entirely, seems to be viewed as of only secondary importance by the biochemist. Carbonic acid rather plays a part in the solution of formed bone tissue. It governs equally the conditions of acidosis and alkalosis of the organized tissue.

The Rôle of Fatty Acid.—According to Klotz, fatty acids, derived from the fats, can play a part in calcification. This is true for certain calcifications, but not for ossification properly speaking.

The Rôle of Proteins.—Another point, generally neglected, should be reviewed. The complex organic substance where calcareous precipitation takes place, does not play the part of an indifferent substratum. According to the nature of the matrix tissue, a selectivity of inorganic salts comes into play. Of this subject we as yet know practically nothing. And the intervention of this new factor in the problem of the calcareous hardening of bone does not simplify it. But it is certain that the deposition of calcific matter, in either crystalline or colloidal form, should be powerfully influenced by the physical or chemical nature of the colloidal substratum in which the deposit is made. No one has ever been able, it is true, to disclose precisely the combinations of calcium with organic albumins. On the other hand, at least for the plasma, it has been shown that inorganic phosphate is quite susceptible to ultrafiltration, hence it is not bound with proteins.* (Rona, Freudenberg and Gyorgy). It is likely, although not demonstrated, that this is true also of the phosphates in the interstitial fluids.

Watt recently has attempted to determine the influence of the nature of the substratum on the morphological character of the deposit. The idea was good, but the results obtained seem to permit only doubtful conclusions. One should assuredly retain the idea that the nature of the pro-

*See footnote on page 55.—*J. A. K.*

tein colloidal substratum should certainly influence, either physically or chemically, the deposit of calcium which is made in it.

The conceptions of Freudenberg and Gyorgy are of greater interest. These authors believe that a series of substances, anomalously present in the tissue, can prevent the laying down of Ca. They would be supplied by autolysis and the physiological destruction of albuminoids; these are, for example acid amines creatinine, guanidine, ammonia salts, urea, etc. In a tissue of normal physiological exchange, no fixation of calcium will take place. This is only produced when metabolism is modified.

Without stating precisely the exact nature of the bodies which prevent the union of Ca and living tissue, one should compare this idea to the conception that we have advanced in the preceding chapter, on the rôle of the cells. Living, the latter oppose calcification. Dead, they no longer prevent the deposit of calcareous salts and calcifications may take place. Research shows, in short, that only dead tissues, or those with a very much reduced vitality, are capable of fixing calcium.

In the eyes of the biochemists, fixation of calcium by the proteins of the tissues is the first stage of ossification. The second would consist in a combination of this complex protein-Ca compound with carbonate, and especially with phosphates. In this conception there would be first a chemical union of Ca with the organic substratum. After this has occurred, the resulting complex calcium-protein compound combines with inorganic calcium salts, phosphates and carbonates. Freudenberg and Gyorgy have especially applied their theory to the exposition of the pathogenesis of rachitis.

This conception still remains very hypothetical. But it is none the less true because it is in accord with histological observations. The latter show a stasis of interstitial lymph in the tissues in process of ossification, hence a slowing of

exchange. Now, at the very foundation of the conception of Freudenberg and Gyorgy there is precisely a sluggish exchange between the blood and the tissue to be calcified.

Rôle of Mechanical Factors.—The influence of mechanical action seems to be beyond doubt, but their more intimate mechanism is still unknown.

Calcium deposition in ossification is a colloidal deposit which is made in another colloid, the pre-osseous hyaline substance. Now, mechanical forces (traction, pressure) are capable of modifying the deposition of colloidal substances. It is in this way, without doubt, that they have their action in ossification. In the path of traction, for example, the colloidal deposit of calcareous material will differ from that at the points where such traction is not exercised. The protein-calcareous particles will be smaller there and consequently the bone more dense and better from the functional point of view.

These are but hypotheses, but they conform with all that we know today of the physicochemistry of colloids.

Rôle of Nutrition.—Up to the appearance of recent American works on rickets, the influence of nutrition was thought to be a commonplace thing on which there was no occasion to insist. The researches of the schools of McCollum and of Pappenheimer, in defining the influence of the fat soluble vitamine, have shown that nutrition plays a part of capital importance in ossification. Absence of this factor brings about rickets. Without this humoral element, calcium fixation is impossible.

Rôle of Light.—The same researches have shown that the absence of light also prevents the fixation of calcium and leads to rickets. It suffices to expose animals to the sun or to ultraviolet rays to demonstrate that despite the deprivation of vitamine, fixation takes place normally.

Rôle of Endocrine Secretions.—Do endocrine influences play a part from the standpoint of calcium fixation? It is certain that the thyroid, testicle, ovary, and thymus are of

considerable importance in the growth of bone and in the mechanism of its repair. But we do not know how they exercise their action. The suppression of the thyroid in the growing period stunts animals, while removal of the testicles makes giants of them, but we do not know why. On the other hand, in the adult animal there is great difficulty in perceiving the action of the glands of internal secretion on bone repair.

From this it is obvious how much more complex the phenomena of calcium fixation are than one could have supposed them to be.

II. HISTOPHYSIOLOGICAL CONDITIONS OF CALCIFICATION

When one studies regions of ossification, he is struck by discovering signs of resorption of pre-existing bone in these cases. Resorption and osteogenesis always appear adjacent to each other, and it may be asked if there is not in their juxtaposition a true law of ossification.

In the first place, let us view the facts. On studying the relations of callus and of the end of a diaphyseal fragment in an aseptic fracture, true zones of bone rarefaction are discovered in the vicinity of the deposit of new bone around the old diaphysis.

In the midst of the ossification which surrounds the ends of amputation stumps, one finds also a rarefaction of the diaphysis. In ankyloses, below the new bone which appears in the interspace and which welds the epiphyses, there exists an intense rarefaction at the level of the former subcartilaginous zone. This zone of rarefaction can always be found in operations for ankylosis. In neurotrophic arthropathies the same conditions are present. Neighboring rarefaction and formation of new bone is a commonplace phenomenon.

There is then occasion to inquire if the two phenomena are not related, and the idea presents itself that the cal-

cium freed at one point is utilized nearby. It would have there a local calcific mutation. But if this is so, it is necessary that the interstitial fluids about zones in process of resorption and ossification should be rich in calcium. This fact is not yet demonstrated. It seems to be the nodal point of the chemical problem of ossification.

This calcific surcharge is unstable. Calcium materials, in a state of saturation, dispose themselves on the preosseous framework present in the territory under consideration. There is thus transport of calcium from one point to another. Between old bone and new bone, a tendency to equalization is noticed.

When one seeks to define more closely the intermediary mechanism in the creation and the results of this local calcific surcharge, he is necessarily led to suppose the existence of a soluble form of calcareous material which is diffusible for a slight distance. The conception that there is a soluble calcium which intervenes powerfully in the extensive progression of ossification, appears to be beyond dispute. But as soon as one endeavors to specify the phenomena, one immediately encounters difficulties which are as yet unsurmounted. The problem has not yet passed from the domain of histology to that of physicochemistry. Very recent microchemical works, for example, those of M. Prenant and de Cretin, from this standpoint open some interesting vistas.

To the matter of local calcific mutations is related an idea of great practical importance, advanced by Ollier, that of the effect of the presence of bone.

Ollier observed that "tissues which do not ossify when they alone are irritated are susceptible to being ossified when they are irritated at the same time with bone tissue." Is not that like a prevision of the observations recorded above? The effect of the presence of bone is understood as a necessity for the resorption of calcium in the vicinity

of a tissue to be ossified. It is only a particular case of local calcific mutation.

Unfortunately Ollier, who delivered this law empirically, did not realize either its considerable importance in bone physiology or its especial mechanism.

Bone intervenes, not by virtue of a mysterious effect of its presence, but simply because it brings forward indispensable calcareous materials which would be lacking in its absence. In order that the effect of its presence be manifest, bone should undergo resorption. The calcareous materials which it thus frees in the local fluids will impregnate the prepared connective tissue and will be one of the reasons for its passive ossification.

It has been thought that this action of bone by virtue of its presence represented in short a consummation of the processes of bone tissue culture in connective tissue regions which had been prepared by irritation. This conception is unsustainable, since fragments of dead bone and non-osseous calcified masses can play the same part.

The best demonstration of the utility of bone resorption in the mechanism of ossification is furnished by the study of surgical subperiosteal ossification. It is well known that in order to obtain the result sought for in subperiosteal resections one should leave thin slivers of bone adherent to the periosteum. Ollier thought out this technic for the purpose of better protecting the supposed subperiosteal osteogenic layer, in which he saw the specific and necessary element of bone secretion. The fact is rigorously exact: periosteum does not become bone unless there is a little bone on its deeper aspect, and it is on that point that all the work of Ollier rests. The matter is explained otherwise than he had imagined. These slivers of bone die rapidly, and it is their dissolution which furnishes the calcareous materials to the periosteum which has become ossifiable. It is due to their contact, but after their death, that the new bone is developed. The histological appearances

leave no doubt on this point. One can find them in process of resorption in the center of newly formed bone. Here again, bone resorption and osteogenesis appear indissolubly linked.*

In the domain of bone disease, this notion of local transport of calcareous substance comes into play actively and is constantly observed. It is exceptional to find bone rarefaction without noting in the vicinity a certain degree of new bone formation. It is above all in the inflammatory diseases of bone, whatever their nature may be, that this phenomenon is seen. In osteomyelitis the constant contiguity of living and dead bone has no other explanation.

In short, everywhere and in all circumstances, new bone is built in part from the debris of old bone.

III. ROLE OF THE CELLS IN CALCIFICATIONS

As in the case of the pre-osseous substance, the deposition of calcareous materials has been considered the function of the osteoblasts. It appears that this rôle should be retrenched. There is, however, occasion to examine it.

This intervention has been viewed in two ways: direct secretion of calcium, and the freeing of substances governing the deposition of calcium.

In the cytoplasm of the osteoblasts one notes at times vacuoles or granules, generally basophilic. They have been considered as being of a calcareous nature, and some investigators have wished to see in them proof of the secretory rôle of the osteoblast. In reality, these basophilic grains are degenerating forms, capable, as is frequently the case, of fixing lime salts which are superabundant in their surroundings.

*It is possible that the small slivers of bone removed with the periosteum do not die as is stated above, but that they remain alive and act as nuclei around which new bone is formed. Contrary to the authors' theory, a local calcific surcharge arising from the dissolution of these minute slivers cannot furnish sufficient calcium for the formation of an entire new shaft of bone.—*J. A. K.*

Histological study, on the other hand, shows clearly that between these cells held responsible for the secretion of calcium and the calcified zones there is generally an interval of uncalcified pre-osseous hyaline substance. This is obviously in contradiction to the hypothesis of secretion.

The rôle of the osteoblasts in the secretion of calcium is not admissible today.

The action of the cells exerts itself in still another way. They can secrete during their life or liberate on dying, substances which impregnate the fundamental pre-osseous substance, and render it fit to fix lime salts.

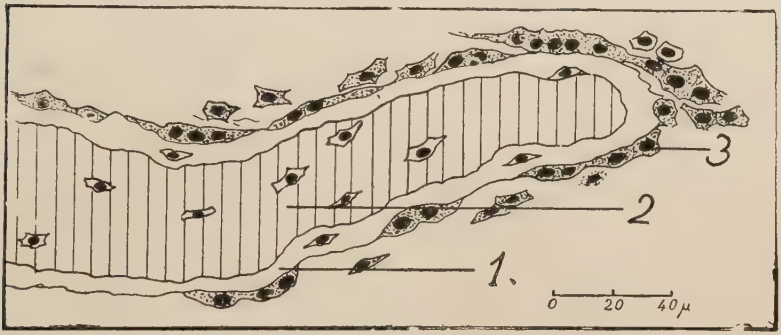

Fig. 9.—Diagram of a site of bone growth (bone 47 days old). *1,* Zone of pre-osseous substance. *2,* Calcified substance, with scant cells. *3,* Osteoblasts.

Robison and his collaborators thus thought that the osteoblasts secrete a ferment capable of decomposing the complex calcium phospho-hydrocarbons present in tissue in process of ossification, the hexose-monophosphates of calcium. Under the influence of monophosphoric ethers there would be decomposition of these hexose-monophosphates of Ca with freeing of an ion of PO_4 which leads to a precipitation of Ca phosphate in the fundamental substance.

With every reservation on its actual value, this conception accords in every case with histological facts.

When the cell is very vital, when its metabolism is very active, the fundamental matrix has no tendency to calcifica-

tion. The chemical reaction of ossification has its equilibrium broken in the sense of a dissolution of the phosphates of Ca. When the cell, on the contrary, has more reduced activity, and above all when it degenerates, the matrix tends to calcify. The equilibrium of the reaction finds itself broken in the direction of precipitation.

Thus, each bone cell exercises an influence on the immediately adjacent surrounding medium. To employ anthropomorphic but convenient language, one can say that this influence appears to be in a sense a struggle of the cell against calcareous infiltration. The result of this struggle is the function of the activity of the cell.

IV. SIGNIFICANCE OF CALCAREOUS DEPOSIT

In reality, the accumulation of calcareous substances in dead organic material is a commonplace phenomenon. All the intraorganic calcifications have the same origin. As soon as a region is deprived of its living cells, even by the death of the latter, there is to be seen an accumulation of calcium materials, on the condition, be it understood, that these exist in the surroundings. Calcareous deposits thus have been noted in necrotic tissues such as tuberculous caseation, in dead fetuses (lithopoedions), retained placentas, in the degenerated parts of vessels, in old fibrinous deposits (phleboliths, calcifications of pleural deposits), divers necrotic elements (prostatic and chorioid concretions), the walls of cysts, etc.

It has been thought that the general increase of the calcium content of the ageing organism is an example of this general law.

The precipitation of calcium materials by the pre-osseous substance appears to us a simple particular example of this great general process. It is because the cells, old fibroblasts which have changed into osteoblasts and decreased in activity, degenerate and die, that calcification takes

place. Here we are far from the function of calcareous secretion by the osteoblasts.

This distinction has been attempted, that, in tissue without cells, only calcification takes place, that is to say that there are laid down crystalline salts of Ca, and not bone. The intervention of the specific osteoblasts would transform the deposit into a colloidal one and cause bone to appear. In reality, between calcification and ossification there is a difference only of degree and not of nature. Our organism incorporates the calcium from external surroundings. The cells struggle against this invasion. Calcium is deposited in places where cellular life is least active. Where cells are numerous, young, and active, the mineral ash is very little and calcium is rare. When, in the course of life, the cells decrease in their activity, calcium tends to infiltrate in the regions which they control. Calcareous infiltration of a tissue is a sign of senescence.

CHAPTER IV

BONE RESORPTION

Despite the apparent fixity of its characteristics, bone is an extraordinarily unstable tissue. It is susceptible to rapid dissolution. It resorbs readily.

It is important to examine the process of bone resorption, to study its signs, its mechanism, the nature of the tissue which arises from it, and to seek for its general import.

I. SIGNS OF BONE RESORPTION

Bone tissue in course of resorption has histological, macroscopic, and radiographic characteristics.

A. Histological Signs of Resorption

The resorption of the bone trabeculae begins at their periphery. The attack is not interstitial but concentric, at least among the higher vertebrates, in both spongy and compact bone. The evidence of bone resorption is an enlargement of medullary spaces and of the Haversian canals, which is brought about by diminution of the calcified framework. The old terms of medullarization and lacunar absorption express these characteristics.

The word medullarization, frequently used by surgeons, is an undesirable term, which should be abandoned. Medullarization is not of itself a phenomenon of absorption, but is its consequence. It suggests also the idea of an augmentation of the hematopoietic content of the connective tissue spaces of bone, a phenomenon which customarily does not exist. Finally, resorption is more often peripheral; the term medullarization makes one think of a central process.

In compact bone, enlargement of the Haversian canals is the dominant sign of bone absorption. In embryonic bone there is apparent, above all, a progressive diminution of the thickness of the bony trabeculae. These two phenomena are of the same order.

Further, the presence of essential elements, the osteoclasts, form an index of bone resorption. When osteoclasts are present there is resorption.

This is always accompanied by circulatory increase. In the enlarged Haversian canals the vessels appear larger. If, experimentally, one brings about increase of circulation, bone in the epiphyses is resorbed to the extent of detaching itself from the investing cartilage and becomes very friable.

The histological diagnosis of rarefaction of bone tissue is at times extremely difficult and occasionally impossible. Histology does not permit us to establish the meaning of a process. When one notes that a bone is rarefied, with enlarged medullary spaces, it may well be a question of condensation of bone originally more rarefied or of rarefaction of a bone originally more condensed. As a matter of fact, only direct observation, aided by serial radiography, permits us to state that a bone is rarefied or condensed.

B. The Macroscopic Signs of Bone Resorption

The macroscopic characteristics presented by bone in process of resorption are dependent on those which we have just stated.

Because of the decreased thickness of the bone trabeculae, bone in process of resorption becomes softer, even to the point of being readily cut with the knife or scissors.

Increased vascularization manifests itself in a very great capacity for bleeding. Normal compact bone scarcely bleeds at all when attacked with the gouge, but cutting the same bone while it is in the process of resorption results in a free hemorrhagic oozing on its cut surface.

C. Radiographic Evidence of Bone Resorption

The shadow of bone which is being resorbed is much less dense than that of normal bone. It is gray, diffuse, and lacks sharp outlines. The trabeculation does not have the usual arrangement. Its architecture appears to be upset.

It is regrettable that systematic research has not yet permitted the determination of the relationship between the radiographic image of a bone with its histological condition. There is here a gap which it would be of great interest to see filled were it possible.

II. MECHANISM OF BONE RESORPTION

Resorption of bone tissue takes place by means of two distinct mechanisms, osteoclasis and osteolysis.

The distinction is old. Volkmann envisaged *lacunar erosion* (actual osteoclasis) and atrophy by *halisteresis* (osteolysis); this term was first employed by Kilian, but only in the macroscopic sense.

A. Osteoclasis

The oldest known and most generally considered mechanism is associated with the intervention of a special element, the osteoclast of Kölliker, the cellular agency of bone resorption.

This is a large cell with several nuclei which are located next to bone at the point where resorption is in progress. The osteoclast is generally lodged in a kind of cavity, a lacuna in the bone substance, which is a result of the corrosion of bone by the osteoclast. These are the lacunae of Howship. They give to the surface of the involved bone an irregular, indented, eroded appearance, which is very characteristic.

Histological Characteristics of the Osteoclast.—These are large cells of from 80 to 100 and more microns in diameter,

with several regular nuclei. The number of nuclei in one cell may vary from 2 to 50. The form of the cell is irregular, and the element as a whole has the appearance of a plasmodium.

In the larger elements, the protoplasm is delicate and has a reticular structure. In the smaller ones, it is denser and generally basophilic.

In the opinion of Jordan, in the cytoplasm in direct contact with bone in process of resorption, there is a dense homogeneous layer which possesses the same staining reactions as does the adjacent bone.

The osteoclasts possess some vacuoles with a lipoid content, and others which are electively stained by neutral red. Their protoplasm also contains mitochondria (Dubreuil), intracellular canals of Holmgren (Retzius), and several centrosomes (Prenant).

At the point of contact with the bone, there is often to be seen the semblance of a ciliated margin (Kölliker), which is particularly visible in the fresh state. Some consider this a border of vibratile cilia which are more or less atrophied. It represents rather a layer of hyaline substance fissured through the influence of the liquid currents. The striation may also have another origin: the visible filaments seem to extend into the interior of the bone substance and there disappear. These are the connective fibrils revealed by decalcification. Their function remains entirely enigmatic. The striated borders are, moreover, far from being constant, and the majority of the osteoclasts are not provided with them. From a cytological point of view they are singular findings, but in reality they are exceptions without physiological interest.

The osteoclasts are elements in hyperactivity. But, according to a general rule, this hyperactivity is such that the cell dies from it. A cell with a very active life is frequently a short lived cell (hypertrophic degeneration). Osteoclasts often present signs characteristic of degenera-

tion: acidophilic condensation, obscure swelling of the cytoplasm, and achromatic nuclei or, more frequently, pycnotic nuclei.

The connection of the osteoclasts with the giant cells of the bone marrow (megacaryocytes) has been the source of innumerable discussions as well as of a great many errors. They are in reality entirely distinct elements. The osteoblasts are connective tissue elements, while the megacaryo-

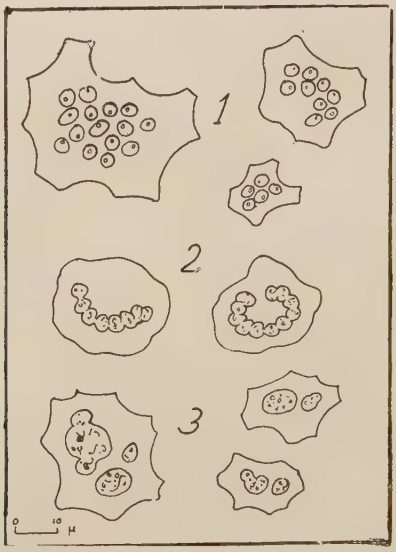

Fig. 10.—Diagram of the polycaryocyte (osteoclast), *1*, of the megacaryocyte (myeloplaxe), *2*, and of sarcoma cells with monstrous nuclei, *3*.

cytes arise from the precursors of blood, and they are myeloid elements which have come to reside in the marrow of bones with the hematopoietic elements, exactly as they may have come to reside in the liver or the spleen. Their structure is different. The osteoclast has manifold nuclei; the megacaryocyte has a single nucleus, but one which is very large and distorted, at least as a rule. Physiologically, the osteoclast is a giant phagocytic cell, the megacaryocyte is not.

The question of the connection between osteoclasts (polycaryocytes), myelopaxes (megacaryocytes), and likewise the sarcomatous cells with huge nuclei, has led to many errors and difficulties in the histology of bone tumors.

Origin of Osteoclasts.—Osteoclasts have been likened to fused osteoblasts (Kölliker, Bredichin, Howell), vascular endothelial cells (Wegner, Schaffer, Moschowitz, etc.), and reticular cells of the marrow (Jackson, Dantschakoff, Maximoff, Jordan, etc.).

These views are not absolutely unreconcilable. The reticular cells and the endothelial cells both belong to the same family. They are of the reticulo-endothelial system. The osteoclasts are connected with this histological family, but lack one of their characteristics, that of fixing certain analine dyes (trypan blue, pyrrol blue), if we can believe the negative results of Shipley and Macklin.

Osteoclasts often result from the fusion of osteoblasts or of their hypertrophic development with multiplication of their nuclei. One does not see mitosis in the course of this development.

Osteoclasts are therefore not elements of a uniform origin. They may arise from fibroblasts, osteoblasts, retico-endothelial cells, and stranger still, from sarcoma or epithelioma cells, strange examples of which have been presented by Phemister.

Mechanism of the Action of the Osteoclasts.—This has been the subject of much discussion. The point on which all are agreed is the slowness of this action, without, however, having very precise facts in regard to it.

It has been thought that their simple pressure on bone could bring about corrosion of the latter (Shipley and Macklin). But how can one reconcile this with the fact that a metallic ligature or plate may be tightly twisted about a diaphysis without bringing about an accentuated resorption. How could "osteoclastic pressure," by mere

mechanical action, cause a resorption of such hard bone? Moreover, what is this strange pressure?*

Does the osteoclast secrete a substance which dissolves the calcium with which it is in contact? Kölliker and Pommer advance the idea of a corrosive acid secretion. It has never been proved.

The rôle of carbonic acid has also been spoken of. Roots of plants grown on perfectly polished marble leave on it impressions which are more or less deep. Botanists (Chemin) attribute this result to the presence of carbonic acid. This interesting observation might be applied to the comprehension of the mode of action of the osteoclasts.

A possible diastatic action has also been suggested. It has not been proved. However, it seems plausible. The osteoclast frequently presents the character of a cell in process of degeneration. Now, the degeneration of a cell is a means of liberating endo-cellular ferments.

In the action of the osteoclasts there is not only calcium resorption, but also destruction of the ossein matrix. The osteoclasts supplant the entire bone, collagenous support, connective fibrils, and combined calcium.

Significance of the Osteoclastic Process.—In short, osteoclasis is a variety of phagocytosis and the osteoclast a variety of phagocyte. This has been denied because these elements do not take up pyrol or trypan blue like other phagocytic elements. This reason is insufficient.

Osteoclasts only rarely show forms of intracellular phagocytosis; but they do sometimes unquestionably show them. Jordan has observed in the osteoclasts of the maxilla of the cat the intracellular presence of debris of resorbed bone. We have often noted that the osteoclasts, in the

*There is no question but that pressure can and does cause absorption of bone as is illustrated by the erosion of bones by aneurysms. Not only this, but metallic ligatures are often found to lie loose in a canal in the bone, the canal being lined by connective tissue. The same is true of nails which are driven into bones. The reason the absorption is not more advanced is that the pressure ceases to act as soon as the ligature or nail is loosened. This does not mean that osteoclastic resorption is purely a pressure phenomenon, but that it may be such. It is also possible that the osteoclast may secrete an acid which dissolves the bone.—*J. A. K.*

pathological foci of bone resorption, in man, contain fine bone spicules. These particles must, of course, be small. At times the phagocytosis assumes, as is customary, the extra-cellular form. In this the osteoclast does not differ from other phagocytes.

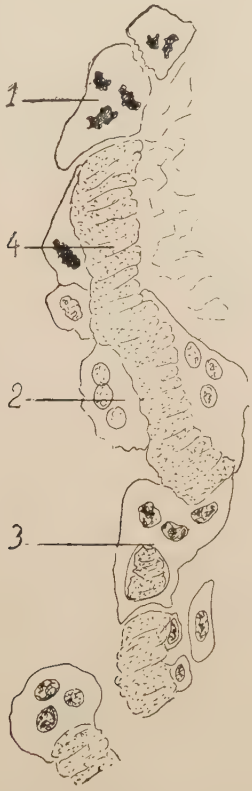

Fig. 11.—Osteoclasts (*2*) attacking a particle of bone débris arising from instrumentation. (*4*) In *1*, degenerating osteoclast; in *3*, osteoclast enclosing a bone particle.

We have been able at times to observe in foci of bone rarefaction, under plates used for osteosynthesis, the phagocytosis of dead bone cells which are completely empty and are indicated only by their wall and characteristic ramified appearance. Perhaps this is a matter of dead

cells entirely mummified and calcified. Prentiss has made exactly analogous observations. In short, in osteoclasis the bone cells disappear. On the other hand, in osteolysis they revert to connective tissue cells; at least a certain number of them do.

One finds a new proof of the phagocytic rôle of the osteoclast in studying what takes place about ivory pegs implanted in bone, which are, in consequence, true foreign bodies (old observations of Flourens, Billroth, etc.).* One finds here spaces in which osteoclasts have accumulated. Likewise, osteoclasts are found in nonossified calcified masses which they attack and in which they make lacunae.

The Ultimate Fate of the Osteoclasts.—After fulfilling their function, what becomes of the osteoclasts? In the opinion of Kölliker they revert to osteoblasts; in the opinion of Jackson and Arey they become reticular cells. In the opinion of others (Jordan, Maximoff, etc.), osteoblasts are irreversible elements and cannot again return to their original form.

We have the same impression: we have always seen the numerous osteoclasts which are found beneath the metallic plates used for osteosynthesis degenerate and disappear.

B. Osteolysis

Resorption of bone does not take place exclusively through osteoclasis, as many historians and pathological anatomists believe. Truth to say, the mechanism of osteoclasis is a relatively accessory one and its significance somewhat special. The disappearance of bone takes place generally without apparent intervention of cellular elements. The bone trabeculae diminish progressively in

*It may seem that the author is confusing the osteoclast with the foreign body giant cells such as accumulate around ivory pegs. However, it may be that the osteoclast is really nothing but an ordinary foreign body giant cell which happens to be located in the bone. If this is true then the osteoclast would probably differ from the osteoblast, as the foreign body giant cells are believed to arise from the wandering phagocytic mononuclear cells of the connective tissue, while the osteoblasts are believed to arise from the fixed connective tissue cells (fibroblasts).—*J. A. K.*

thickness, the Haversian canals enlarge without one's finding osteoclasts in the least. The phosphocalcareous complex purely and simply disappears without any special cells participating in this process. The calcium phosphocarbonate disappears, like the glycogen of the hepatic cell or the fat of the adipose cell.

This osteolysis takes place exclusively under the influence of humoral processes, which it is necessary to state precisely.

It must be studied in circumstances in which it is found in a relatively pure state, that is to say, in certain pathological processes, such as fibrous osteitis (in Paget's and Recklinghausen's diseases). One may thus acquire a feeling of its importance. In returning to normal ossification, one sees that there it plays a fundamental part which up to the present has been neglected.

Histological Characteristics of Osteolysis.—The description of it is singularly easy, since this process of bone resorption is characterized by the absence of the intervention of any apparent cellular process. Bone "breaks down" and the fundamental connective tissue framework reappears in its place. Microscopically, one notes only an enlargement of the medullary spaces or the Haversian canals, without the presence of osteoclasts.

This osteolysis is a resorption, not of the entire bone, but of certain of the elements of the phosphocalcium complex and of the pre-osseous substance. The collagen matrix remains.

It seems to take place all at once. Everything disappears suddenly. In fact, in certain cases, when the mechanism is less rapid, one can distinguish two stages: the calcium disappears first, the pre-osseous substance later.

In these cases, between the areas of bone substance which have not yet been attacked and the true connective tissue of the medullary space, there is seen a slender band of pre-osseous substance, hyaline. It is moreover impossible to

distinguish these histological forms of resorption by osteolysis from those of the formation of bone. This is easily understood. Physiological evolution alone indicates the significance of the phenomenon and permits the interpretation of the histological form.

Chemical Mechanism of Osteolysis.—Osteolysis is a true disintegration of bone which reverts to connective tissue. It is logical, therefore, to seek the explanation of the taking up of these materials in the chemical mechanisms which have brought about the precipitation of the pre-osseous substance and of the calcium complex. It is only a rupture of the chemical balance of the phospho-carbonates of lime, in a direction inverse to the fundamental ossifying deposition.

It should be regarded as the result of an increase of the soluble phase through the rupture of the fundamental reaction of ossification.

Phosphates of Ca ⟶ Free ions ⟶ Phosphates of Ca
insoluble ⟵ Ca and PO_4 ⟵ soluble

What is the cause of this rupture of balance in the direction of increased solubility of the phosphocarbonates? This is a very obscure physicochemical problem allied to the whole question of the humoral equilibrium of the blood (C. Blum) and especially of the plasma.

The influence of the carbonic acid content of the blood and of the interstitial plasma, the ionic acidity of the medium, have been advanced in an attempt to explain osteolysis. They are certainly very important. They explain those "toxic atrophies of the bone," those "osteomalacias" noted in a large number of intoxications by phosphorus, adrenalin, mineral acids, etc.

Long before acidosis was studied as a humoral condition, the clinical researches of P. Ferrier had demonstrated the action of therapeutic "acids" on bone and calcification in general.

The change of the content of the medium in free ions of PO_4 and Ca, whatever its physicochemical mechanism, may

be induced by an action of the cells. Thus are bound together, at least hypothetically, the chemical processes and the histological position. The bone cells as a result of a change in their metabolism would cause a modification in the surrounding medium which they control. This modification would lead either towards a dissolution of the phosphocarbonates of Ca (histological hyperactivity), or towards a precipitation of these same bodies (cellular hypoactivity).

Connection Between Increased Circulation of the Blood and Osteolysis.—Important relations connect resorption of bone by osteolysis with increase in the circulation of the blood.

If by any process whatever the activity of the circulation is increased in the vicinity of a bone, the latter becomes rarefied. It changes neither in chemical composition nor in its fundamental histological structure. It changes only quantitatively in relation to that of the connective tissue. The medullary canals increase and the bone trabeculae diminish. The architecture of the bone is modified, but not the chemical structure of the bone substance present in the tissue: in the bone trabeculae which remain, the structure and composition are the same; only the size and number are diminished.

Inversely, blood or lymphatic stasis in a connective tissue area favors ossification.

This effect of the circulation on the deposition or removal of bone is very general. It is also found in calcifications which are not specifically bone. One may cite here, among others, interesting observations by Lick. In studying the calcifications and ossifications that take place in the kidney of the rabbit after ligature of the renal artery (classical experiments of Sacerdotti and Fratin), he has shown that with a too active circulation there is neither calcification nor ossification. With a slowed circulation there is only necrosis and very slow calcification of the

regions affected by necrosis, ossification being nil. An extremely precise adaptation of the blood supply to an area of connective tissue is therefore necessary in order that formation of bone trabeculae may take place.

In surgical pathology, the rôle of increased circulation in bone rarefaction is likewise very clear. One can give numerous examples of it. Here are three:

When callus which is already formed is suddenly resorbed as is sometimes seen, one may generally find an inciting local cause of hyperemia as the origin of the clinical resorption. We have seen, for example, a callus which had been noted radiographically for several months become suddenly resorbed during an attack of influenza which had caused redness, fever, and several drops of pus beneath a plate used for osteosynthesis.

Likewise, we have seen periarterial sympathectomy followed by an acute resorption of callus which had been noted radiographically and macroscopically in the femoro-tibial epiphyses of the knee.

Finally, the most typical example is that of the repopulation of bone grafts. As long as the Haversian canals are filled with dead connective tissue, the graft is not changed. But, little by little, these canals are reinhabited with living tissue, with true granulation tissue which is richly vascularized. The enlargement in the Haversian canals begins immediately.

From a practical point of view, only well vascularized bone, that is living bone, is capable of being quickly resorbed. When a bone graft disappears gradually, it is because the union has taken place between the graft and the tissues of the host, because, in short, the graft has "taken." When this "taking" has not occurred, the bone is not changed. It is an inert foreign body which is slowly attacked by osteoclastic phagocytosis, and the erosion occurs only at its periphery. By an erroneous interpretation, surgeons often consider a graft as having taken when it is not

resorbed. Inversely, when the graft is resorbed, they attribute this result to poor nutrition. This is exactly the contrary of the truth. The best sign of the taking of a graft is found in its rarefaction and disappearance.

In an analogous way, it is interesting to draw attention to the following facts. The osteoporosis of the fragments in a pseudo-arthrosis has often been reported as a lesion of the nutrient artery leading to a decrease of the circulation, hence of the nutrition of the bone. The nutrient artery has nothing to do with this phenomenon. Osteoporosis is connected with an increase of the circulation of bone tissue and not, as is often said, to vascular disturbance interfering with the supply of nutrient material necessary for the skeleton. Mature bone needs only a very small blood supply. Its metabolic needs are very insignificant.

In addition to the examples given above, the influence of arterial anemia has been directly studied. Grey and Carr have observed that neither arterial anemia nor venous congestion lead to bone atrophy. They have not, however, grasped the essential mechanism of this atrophy. But their negative results are the more interesting because of this.

In some instances the exact rôle of the circulatory activity may be masked. An increase of the circulation leads to bone resorption, but through the freeing of calcium and the creation of a local calcific excess, new bone can be formed. There will then be *histological* atrophy of the bone tissue and *anatomical* hypertrophy of the bone as a whole. This double process in hypertrophic resorption is extremely frequent. It dominates bone pathology, and we shall have to view it more closely from this standpoint.

The notion of bone atrophy through insufficient blood supply is very widespread and deeply rooted. It is the basis of numerous pathological errors and should be definitely abandoned.

In short, it is facts of this order which are probably at the bottom of those still obscure and peculiar phenomena

of bone production, or more often of bone rarefaction, which occur after lesions of the nervous system. In the case of bone as in all other tissues, it is necessary to view trophic disturbances as essentially vasomotor disturbances.

It is these vasomotor disturbances, especially vasodilatation, which explain the loss of weight, size, increase of organic material, and decrease of the mineral matter content of bones which may be observed following nerve section. It is unnecessary to suppose, as D. Garing does, the existence of special hypothetical trophic fibers for bone.

C. **Relationship of Osteolysis and Osteoclasis.**—We have seen that osteoclasis is a phenomenon of ordinary phagocytosis which is exercised on all of the bone elements, whether they be living or dead. Osteolysis, on the other hand, is a humoral phenomenon which affects only ossein and the mineral matter, and influences only living bone.

The two processes, absolutely distinct in their pure form, may be combined in different ways.

In young bone especially, certain observations permit us to envisage an indirect intervention of the cells present: fibroblasts, osteoblasts, or bone cells.

As far as the osteoblasts are concerned, we have indicated above that a part in the destruction rather than in the formation of bone might be attributed to them. The osteoblast would be a form of reaction of the connective tissue cells to calcium invasion.

The rôle of the bone cell appears absolutely clear in certain cases. In bone of young type in process of resorption one sees typical bone cells everywhere, the calcified substance becomes faint and disappears, leaving the connective tissue matrix in place. There is here nothing resembling osteoclasis, that is, phagocytic action. The bone cell, resuming its activity, seems to cause the calcific material to disappear. It resumes the aspect and function of the osteoblast. In reality, in spite of this cellular intervention,

it is still a matter of osteolysis. Here the cells do not act directly, as in osteoclastic phagocytosis. Between the two forms of bone destruction, intermediary forms may evidently be found. Certainly there is no gulf between them, but, practically they are different enough to justify our placing them in special categories.

It is a long time since Rigal and Vignal, in a classical treatise, noted that in resorbing callus the cells were hypertrophied, with prolongations which were likewise distended. Around these hypertrophic cells the fundamental bone substance presented a zone which was distinctive in appearance. Rigal and Vignal recognized that the bone cells, resuming their activity, play an important part in the resorption of the osseous framework of the callus. We are of exactly the same opinion.

This interstitial osteolysis seems peculiar to bone of a young and primitive type. It is very rare, and even generally absent in compact bone. In these cases it takes place only at the periphery, never in the center of the bone, as it does in the interstitial type. Thus the rarefaction of bone, produced almost exclusively by osteolysis, operates quite slowly on the bone of adults, while at times it takes place with a rapidity truly unbelievable in bone of the young type: callus or bone of the lower vertebrates. In highly differentiated bone, such as the compact tissue, the bone cells, withal few in number, appear too highly differentiated, too well adapted to be able to take on a great activity.

In summing up, the cellular elements of bone tissue, bone cells or osteoblasts may intervene in an indirect way in the process of osteolysis. This intervention does not take place by phagocytosis as in osteoclasis. The histological picture presented recalls rather the phenomenon of lysis by the secretory action of neutrophilic leucocytes. Here the action of the cell is a particular example of this more general metabolic control that the bone cell or the osteoblast exer-

cises on the interstitial substance which surrounds it. The process is identical, but it is effected in inverse order. It is revealed in osteogenesis.

III. THE CHARACTER OF THE TISSUE RESULTING FROM BONE RESORPTION

After resorption by osteoclastic phagocytosis, the site of the resorbed bone is replaced by the neighboring connective tissue. At the point of resorption osteoclasts, which were the active agency of the process, are often met. Little by little the latter degenerate. One does not see here a tissue arising from the resorbed bone, but a tissue which replaces it.

It is quite different in the case of osteolysis. Bone tissue ceases to be bone, but it persists and becomes connective tissue.

The connective tissue matrix first has the characteristics which it had before its impregnation by the pre-osseous substance and calcium. But when it is a question of a very young tissue, very embryonic, things do not long remain in this state. Rapidly, under the influence of surrounding conditions, the connective tissue again takes up its proper evolution and undergoes a differentiation in a different direction which gives to the replacing tissues new characteristics.

It may become fibrous. The connective tissue spaces are filled by a tissue with a compact and dense collagen framework. However, this phenomenon rarely occurs. It is observed in the evolution of callus, in the formation of fibrous pseudarthrosis, and above all with an incomparable clearness in the fibrous osteitis of Recklinghausen.

In other cases the connective tissue matrix can again undergo bone metaplasia. This very frequent outcome is the essential basis of the *modeling variation* of John Hunter.

Certain cells of this connective tissue can become charged with fat and become adipose.

Connective tissue can finally evolve toward a less normal density and become chondral, and even at times definitely cartilaginous. Those nodules of cartilage which are sometimes encountered in bone in process of formation and in pseudarthroses are formed in this way.

Also in the neoplastic transformation of this freed connective tissue, there may arise those diverse and strange forms observed in bone sarcomata: osteosarcomata, osteochondrosarcomata, ossifying sarcomata, osteoid sarcomata, etc. All these categories, multiplied to infinity by the classifying spirit of the pathological anatomists, the greater part of the time represent only different evolutions, at times seen sids by side, of the connective tissue of bone which has undergone osteolysis.

IV. THE BEGINNING AND SIGNIFICANCE OF BONE RESORPTION

In its last analysis bone resorption is reducible to a break of a physicochemical equilibrium of the colloids which are present in the interstitial plasma.

On this equilibrium, which is less stable than it appears to be, divers factors may have an influence. We know of the following. Are there not perhaps others?

Blood factors (composition and quality of the blood).

Circulatory factor (activity, more or less great, of the interchange in the region considered).

Connective tissue factor (state of the connective tissue, itself governed by the condition of the cells and above all, certain endocrine secretions, such as thyroid, genital secretions, etc.).

Mechanical factor (morphogenic effects of pressure, traction, tangential movements, etc. These effects are exercised more specifically through the medium of the fibrillary framework of the connective tissue).

Every modification of any one of these factors is capable of bringing about a change in the equilibrium of the reaction, hence to provoke, as the case may be, bone deposition or resorption.

With the facts actually known, one can define the results of some of these factors.

The blood factor certainly comes into play in the bone resorptions which accompany conditions of demineralization, for example, the bone rarefaction of osteomalacia, properly so called, the rarefaction of pregnancy, etc. The greater part of bone disturbances in the course of general diseases are governed by this mechanism. Bone appears to be the great calcium reserve of the organism. When there is loss of calcium, the blood, the constancy of composition of which tends always to be maintained, takes it from the skeletal system. To the action of this blood factor there are related the influence of acidosis, disturbances of nutrition, etc.

The circulatory factor has been reviewed at length above. Augmentation of the circulation in the vicinity of a bone causes resorption of the bone. Inversely, under certain conditions, slowing of the circulation is favorable to the deposition of bone substance. We systematically employ this rather vague term of the activity of the circulation. It comprises a great number of modes of action. But, as we are almost completely ignorant of the particular influence of the latter, it appears wiser to employ a term intentionally indefinite. By such modifications of the circulatory system, the nervous system has its effect on the skeletal system. While but slightly accentuated, this action is nevertheless certain. Bone disturbances observed following nerve lesions of various types, supply indubitable proof of it. There are true trophic disturbances of bone, which are but the result of vasomotor modifications.

The connective tissue factor is still more vague, but to us it appears also to be beyond question. The connective

tissue which is the matrix of bone has not a constant composition or behavior. It varies with the action of a series of influences, among which are hormones, and especially the thyroid hormone, which acts so powerfully on connective tissue metabolism.

By mechanical actions, the morphogenic actions of Wolff, of W. Roux, of Triepel, the effects of use and of lack of use, are explained. A mechanical action, traction or pressure acting constantly in the same direction, would have an important influence on the arrangement and the quantity of the connective tissue fibrils of the matrix. However, it is the character of the connective tissue, i.e., bone matrix, which determines the histological form of bone. Ultimately, the morphogenic action is exercised especially on the collagen framework in spite of the bone infiltration which invades it.

The influence of purely mechanical action on a chemical phenomenon should not surprise us when it takes place in a colloidal medium.

Thus bone appears to be subordinated to a great number of influences which tend to make it disappear. There is a perpetual struggle for the maintenance of a tissue which seems to be eminently stable. As soon as the equilibrium is broken in some way, resorption comes into play and originates the series of modifications of which we have just spoken. The phenomena of resorption appear to be of the first order in skeletal physiology; they dominate the pathology of bone.

Nothing can be understood about either the one or the other, if one is not imbued with those ideas of which we have just spoken. Therapeusis also should be inspired by it. We shall know how to deal with bone tissue only when we shall know precisely the means of dealing with this resorption.

These considerations permit us to go higher and to approach the question of the general significance of bone.

With our attention centered upon ourselves, we would fain conceive that bone is present to permit our movements. This is only anthropomorphism. Bone represents above all else the seat of reserve calcareous salts. The organism cannot dispense with them. A precise amount is necessary for it, neither too much nor too little. Conformable to the regulation of the maintenance of the constancy of its composition, the blood tends to contain a fixed quantity of calcareous material. When its calcium content tends to be lowered, it draws on the calcium in reserve, that is to say in the bone tissue.

Inversely, when the calcium content augments, it relieves itself of its excess by depositing it in bone.

As paradoxical as it may appear, the rôle of support is only in a sense a secondary one, when the subject is viewed from the standpoint of the general physiology of tissues. From the point of view of the individual, the function of the calcareous reserve, which is unknown to all of us, appears to be secondary. To our way of thinking, that which dominates in the skeleton is mechanical function.

These general considerations are not peculiar to bone tissue. One can draw analogies for adipose tissue. From the standpoint of tissue physiology, adipose tissue is a means of placing in reserve the neutral fats in excess of the blood. It is thus something which one might call a balance wheel for the fats. In the same manner bone tissue is a balance wheel for calcium. But for the organism as a whole, adipose tissue still serves as an organ of protection against cold, or again as an elastic cushion. Despite its considerable importance to the organism, these are, from the standpoint of general biology of tissues, only accessory functions. It is as if there were a utilization of a functional by-product. But is it not known that in industry the by-product of manufacture often takes, little by little, a greater importance than the original product?

CHAPTER V

THE PRESERVATION AND FUNCTIONAL ADAPTATION OF BONE

It is impossible to treat of the physiology of ossification without viewing, at least in brief, the question of the *morphogenesis* and the *functional adaptation* of bone, the question, so to speak, of the genesis of the forms and structure of bone.

But this is a large question, the exposition of which alone merits a great many pages. Conformable to our general plan, which is rather to study general processes than detailed facts, we shall deal here only with the fundamental mechanisms which govern bone adaptation. We consider the latter as proved. For the study of detailed facts we refer to the classical works of Marey, Wolff, Wilhelm Roux, etc., and to the recent monograph of Walther Müller (1924).

We shall examine successively the histological mechanisms of adaptation, the combined mode of action of the intervening factors, the intimate mechanism of their influence, and the limits of the morphogenetic action.

I. HISTOLOGICAL MECHANISM OF THE ADAPTATION OF BONE TISSUE

Bone which has just formed is of a coarse type. It is composed of narrow trabeculae, giving, by their grouping, a system with large mesh without definite orientation. How can this imperfect, rough model, with rudimentary physiological properties, produce tissues as solid as adult bone?

Four processes come into play: strengthening of the existing trabeculae, their resorption, the creation of new trabeculae, and the limitation of the extension of the latter.

A. Strengthening of Existing Bone Trabeculae

This strengthening takes place by the method of apposition. Against a completely formed column, there is deposited new bone substance in the form of thin lamellae. Each of these comprises a matrix formed of a close network of fine connecting fibrils, generally arranged in a definite way which is determined by the predominant mechanical force, and of a mass impregnated with preosseous hyaline substance. All of this material calcifies.

In general, apposition of new bone is made in a continuous way. But the fibrils vary in their arrangement, from the very moment of their formation. It is because of the variation of direction of the fibrils that the different bone lamellae can be distinguished. In reality, the lamellae are but slightly differentiated regions in a continuous whole.

The deposition of bone substance against the primary trabeculae occurs in a more or less active manner. When the deposition is reduced and irregular, the connective tissue spaces remain large: this is the case in spongy bone. When the deposition is considerable, and well ordered in the sense of being in a single direction, Haversian systems are obtained.

The deposition of bone can also take place on a series of calcified formations: Sharpey's fibers, in the case of bones called membranous (bones of the skull), or trabeculae of calcified cartilage in developmental cartilage (guiding columns). The idea of the *directing column* (travées directrice) is important in morphology. Primitive bone trabeculae, Sharpey's fibers, and the columns of calcified cartilage give the impression of governing ossification. One can perhaps criticize this classical term; however, it is convenient and deserves to be preserved in spite of its evident bad quality.

Such are the great lines of the transformation of primitive and still imperfect bone into definitely compact bone. But in reality, between the point of beginning and the

termination, there is a kind of hiatus in our knowledge. We take account of the general way in which this transformation operates, but we do not know the changes in detail. In particular, we are completely ignorant of the reasons for the arrangement of connective fibrils in the successive layers of bone apposed against the primitive trabeculae.

Pathologically, the processes of bone condensation are related to a mechanism of the same order, but these also are little known.

Eburnation is spoken of constantly. It is known what this means from the macroscopic point of view, but the phenomenon in itself has not been studied. Very attentive in studying this, we have not attained a true grasp of its mechanism. It is certain that bone eburnates; that is to say, bone becomes changed in such a way that it resembles ivory and is of very little vascularity. Macroscopically, this is bone which does not bleed. On section the Haversian canals are of very small caliber. But is this a cause or an effect? One thing is certain: this eburnated bone is bone of anatomical repair, that is to say, one which is found in abnormal conditions. It is observed in three principal circumstances: in healed rickets, in the callus of fractures which have suppurated, and in old osteomyelitis with new bone formation. In these conditions bone which is eburnated and apparently identical does not always have the same physiological properties. Rachitic bone is one which is extremely hard, and is very difficult to break. The bone of suppurated fractures sometimes breaks spontaneously from minimal causes. It is a singular thing that the direction of the line of fracture in it is generally transverse, without fissures and without fragments. The observations cited above show how very interesting it would be to study the mechanism of eburnation and the physical qualities of this pathological bone.

The term *eburnation* expresses in a precise manner the

analogy of this tissue with ivory. This similarity appears to be very exact. In the formation of ivory, the vascular ingrowth appears to take place and bone is deposited, but in some way the vessels are rapidly obliterated.

It is necessary to compare the process of eburnation with that which takes place in the evolution of the antlers of deer, where each year, thanks to a temporary vascular growth, a deposit of new bone takes place, and this is soon followed by vascular obliteration.

B. Resorption of Trabeculae

Thus, as we have shown in the preceding chapter, there is an intimate connection between the formation and destruction of bone. Ossification and osteolysis are in continuous balance. All history of morphogenesis rests on this idea which is the modeling resorption of John Hunter. Flourens said, "Continual change of substance is the great and marvelous force in the development of bone."

Certain trabeculae strengthen, others destroy themselves. The combination of these two opposed processes determines the architecture of bone. In spite of its appearances, bone is a tissue without any morphological fixity. It is in perpetual change. A femur is histologically more unstable than a tendo achillis.

One of the points in the organism where these changes are the most evident is the diaphyso-epiphyseal junction.

The combinations of resorption and new bone formation have for morphological evidence the well known aspects of Haversian systems lying within other Haversian systems.

C. The Formation of New Trabeculae

At the same time that the old trabeculae grow and thicken, new ones form, partitioning the medullary spaces and very rapidly changing the bone from a coarsely spongy to a compact state.

Through the formation of new trabeculae and their ultimate growth, the density of the bone is greatly accentuated. This is readily understood, since by it there is a formation of new surfaces for bone apposition. Finally, condensation of bone depends upon the exposure of surfaces available for apposition.

D. The Limitation of Bone Extension

One of the most important mechanisms in the morphogenesis of bone is found in the restraining action which all of the fasciculated tissues exercise on the bone framework in process of extension.

When one studies the development of new bone formation, one sees that at a given time contact between bone and fibrous or muscular elements takes place. The latter seem to place themselves as a barrier across the path followed by the progressive bone metaplasia. Bone abuts against, but can never break through, this barrier.

Fascia and muscular fibers are insuperable obstacles to it. The bone trabeculae turn and bend themselves in the direction followed by the obstacle, along the length of which they seem to glide; never do they traverse it perpendicularly. Fibrous tissue, muscular tissue, and aponeuroses force the bone tissue either to arrest its thrust or to follow their direction.

These ideas are illustrated with particular clearness when one examines the fibrous investment of bones, that is, the periosteum, but one finds them in many other instances. The limitation of the progression of bone tissue is an essential mechanism in the modeling of bone form. It is less in favoring than in limiting its thrust that many mechanical forces act on the bone form.

This arresting action of the fibrous tissue determinants may be explained in a very simple way. It suffices to recall the two following fundamental ideas: first, the essential part played by the connective fibrils in the deter-

mination of the form of the matrix of the bone trabeculae; second, the governing rôle of mechanical action on the determination of the arrangement of these fibrils.

Let us study analytically what takes place in the zone of arrest of bone extension by fascia.

At some distance from the point of arrest, the bone structure lacks definite arrangement. This indicates that no predominating mechanical influence has exercised its directing action on the connective fibrils, which are the groundwork of the bone trabeculae.

On the other hand, at some distance from the zone of arrest, but this time on the fibrous tissue side, these mechanical forces have come into play. They have determined the arrangement of the fibrils and of the connective tissue bundles. These exist, with their definite direction, because mechanical morphogenetic influences have been in play at this point.

Just at the zone of arrest, is found the point where these mechanical morphogenetic influences begin to make themselves felt. Here the fibrils of the bone framework are arranged by these mechanical forces, as are the fibrils of the fibrous tissue bundles and in the same direction. The organized bone framework has the arrangement of the fibrillary network which originally formed it. They probably have the same direction as the fibrous tissue bundles. It is as a connective tissue formation that the bone framework is oriented.

We shall see later that the periosteum has the same origin. It is the limiting membrane of bone.

Such is the explanation of the mechanism of the modelling action of fibrous tissues and the musculature on the form of bones.

Thus, by an interplay of these processes, bone, coarse and imperfect, which is born of connective tissue metaplasia in a given region, is transformed into either compact bone of the Haversian type, or into spongy bone,

properly so called, with thick trabeculae and partitions, which are, from an anatomical point of view, precisely arranged. Young bone grows somewhat like a tumor. But restraining actions come into play: pressure leading to resorption, limitation, and orientation through fibrous determinants. It is these actions which model bone and give it its form and architecture.

We have just reviewed the means by which this transformation takes place. We must state precisely the mechanisms which rule and harmonize the utilization of these modes of action.

II. SYNTHETIC ACTION OF MECHANICAL FACTORS

Without having undertaken systematic research on this question, our personal observations and thoughtful study of previous works have permitted us to form the following ideas which it is interesting to set forth.

In truth, this has not been easy. Few questions are as confused as this one. The reading of the works which have been published on this subject, however interesting they may be, does not immediately give one very clear ideas. One must reflect a long time in order to attain a clear understanding of the essential lines of the problem. This is because the authors have worked in a way that was not sufficiently analytical. They generally confuse the influence of mechanical factors on the primary formation of bone, their influence on the evolution of the formed bone, and on the preservation of its existence. But this fundamental distinction having been made, one succeeds in clearing up the question in a striking way.

We now believe that the problem of the mode of action of the mechanical factors on ossification and bone tissue should be put in the following manner.

One must consider, on the one hand, the action of mechanical influences on the appearance of bone. It is

what may be called, with Maas, the *process of organic growth*, regulating the quantity of bone.

It is necessary, on the other hand, to determine the action of mechanical influences on the maintenance and direction of the growth of bone tissue, properly speaking, on its morphogenesis.

A. The Rôle of Mechanical Actions on the Formation of Bone Tissue

It seems to us that the primary formation of bone is conditioned by the existence of mechanical influences. Our view of this matter has been slightly modified since the beginning of our work.

Classically, it is admitted that in order that bone be developed at a given point a certain mechanical force must be exercised at this point. We no longer consider that this idea is correct. The first bone framework may be developed independently of all strain. It has been possible to obtain (Macewen) the development of bone in connective tissue strips (periosteal) enclosed in glass tubes. These tubes evidently protect the contained tissue against all strain. In pathological states one often sees new bone developed at points where really no force is brought into play. For example, we have seen it develop in the vicinity of splinters lodged in cerebral tissue; at other times experimentally in the kidney. Its development has been noted in the interior of bone cylinders, which are regions protected from every mechanical influence.

Humoral influences control the first appearance of bone. Mechanical forces do not necessarily play a part in the determination of the process. They have not a direct, but only an indirect action, either by bringing about in the adjacent bone of the newly formed tissue a process of rarefaction, this leading to a local calcium excess, or by deter-

mining the orientation of connective tissue fibrils in the network which is to be impregnated with pre-osseous substance.

But the initial formation of bone tissue is not the whole story; it is necessary that it should be preserved. The normal tendency of bone trabeculae is to disappear by osteoclasis of dissolution. However, mechanical influences are predominant in the preservation of newly formed bone tissue.

B. The Rôle of Mechanical Action on the Preservation and Growth of Bone Tissue

The rôle of strain on the preservation and thickening of the bone framework is incontestable. This generally arises from the load carried by bone, an organ of support; the skeleton is preserved through the exercise of this function. The removal of all strain through the removal of all load has a fatal influence on bone structure. Numerous researches have been carried out in this direction, but unfortunately on bone already too highly specialized. It would have been preferable to make them on younger, less highly differentiated bone.

We shall see later that the modelling rôle of mechanical action on structure seems to be limited.

Effect of Continuous Pressure.—The pressure may be of a variable type. It may be continuous and very severe. In this case it seems to cause the bone to disappear. This point has been the object of long discussions. Hüter and Volkmann claimed that very severe pressure prevented bone formation and caused its resorption. Wolff supported the opposite opinion and held that bone increased under the influence of increase of pressure, and vice versa. For example, in the concave parts of a long bone the cortex is denser. The same thing is true of the trabeculae of

spongy bone. On the convex side (less strain) there is a decrease which is inversely proportional to the thickness of the cortex.

These facts, which are advanced in the classic works on the subject, are in reality very complex. Although they may be interesting in regard to the organism considered as a whole, they give less clear information in regard to bone tissue considered as tissue. As has been pointed out in the case of a long bone, the pressure is applied through the medium of a structure especially adapted to the rôle of a buffer, the articular cartilage. A very strong force may be applied through the medium of the cartilage without causing any ill effect. Without the cartilage there would be bone resorption. Applied to a long bone in the direction of its axis, a given strain will be supported without modification of the bone. But if it is applied in a direction perpendicular to the periosteum there will be rapid bone resorption. Bone compressed on a non-cartilaginous surface is extremely unstable.*

Intermittent Pressure.—According to the views of certain authors, Jores in particular, the important thing is the intermittent character of the pressure. A continuous pressure favors resorption. But if this pressure is applied intermittently at long enough intervals, then, during the intervals without pressure, there is proliferation of bone in the exact place where the pressure exerted its effect. If the

*The effect of pressure on bone can be especially well observed in the skull. The base of the skull throughout life presents the impressions of the convolutions of the base of the brain. Up to an indefinite time in adolescence, the convolutions of the cortex impress themselves on the vault of the skull. This is a physiological process, but in the normal adult skull these impressions are absent. Should like impressions be observed in the vault of the skull in adult life, they are always the result of increased intracranial pressure. The theory is that the convolutions of the brain are pressed against the inner surface of the skull. This pressure is a pulsating one and the process observed bears relationship to the erosion of bone sometimes observed where an aneurysm impinges on osseous structures. It is a well known fact that, in the skull, tumors occasionally decompress themselves through complete resorption of the skull. X-ray observation gives some grounds for the belief that the pressure on the inner aspect of the skull perhaps stimulates new bone formation externally. On the other hand, release of intracranial pressure results in practically complete disappearance of the convolutional markings, which suggests also that there is new formation of bone in the thinned areas as a result of diminished pressure. This is a subject which could be most profitably investigated in its relation to the general question of pressure effects on bone.—*S. M.*

intervals are very short, the pressure acts as though it were continuous.

These facts, noted by Jores, seem to us to be connected with local calcific changes. Bone is formed under the influence of a local humoral condition. The pressure which has been applied leads to the resorption of a certain quantity of bone and provokes a local calcium excess. In the free periods, except for momentary pressure, columns of new bone or new layers of bone are formed; they will be resorbed on resumption of the pressure.

Thus pressure in the final analysis seems to be an excitant of bone growth, but through a complex mechanism. It determines first a resorption and a local calcium excess. Then, the pressure having ceased, new bone is formed because of the antecedent absorption and the local calcific excess. But, as we see it, the pressure acts only by preparing the proper medium for the laying down of bone. The latter operates only in the absence of pressure.

We believe that the researches of Jores are of great interest in showing that the essential element of the morphogenesis of bone lies in an alternation of periods of pressure and repose. When there is no pressure, bone is formed; when there is strong enough pressure, it disappears. All bone morphogenesis is bound up with processes which unfold themselves between these two extremes.

But up to the present time the interpretation of these facts has been insufficient. One can understand them only in the light of the ideas that we have advanced.

Shocks.—Very strong and discontinuous strains are represented by shocks. Their influence on bone has been studied by Benecke, Schmidt and Lange, especially. The effects are reduced to a combination of atrophy and neoformation.

The result on the whole will vary according to the predominance of the periods of pressure or rest. What we have explained above has been applied integrally here.

The rôle of shocks has often been advanced to explain a great number of surgical pathological conditions of bone, particularly those which result secondarily from a disturbance of the cartilaginous surfaces, structures normally functioning for the purpose of diminishing shock.

Effect of Slight Pressures.—It would be interesting to determine definitely the minimum pressure capable of provoking the resorption of bone. Unfortunately we have no information on this subject.

What is known is that very weak pressures are capable of provoking resorption.

Certain authors, Rustizky, Pommer, think that increase of blood pressure in a bone may be sufficient to determine osteolysis. If this is true in its entirety, namely, that increased blood pressure brings about bone resorption, it is very difficult to explain such action on the ground of pressure alone. Other phenomena of a humoral order, the action of which seems much more important, certainly intervene.

One should recall here the experiments of Jores, who, after placing rubber sacks filled with water or mercury in contact with bone and thus applying known feeble pressure, always observed bone resorption.

Effect of Traction.—The influence of traction on the condition of bone is still debatable. In the views of Roux and of Weldenreich, traction can bring about bone formation. Consequently *traction bones* should exist. One may cite as examples calcified ligaments and bones of fibrous type. The example of the great trochanter is classical. The researches of Julius Wolff on this subject are familiar. The question merits reopening in the light of the ideas advanced above.

In any case, ligamentous ossifications are generally in relationship with rarefactions of the skeleton in the vicinity. Ollier insisted on this. Holzknecht constantly found relationship between the two phenomena. Ligamentary ossifications are always secondary to skeletal destruction.

Effect of Shearing Forces.—By shearing action is understood the combination of pressure (or traction) with tangential strain.

Since the works of Roux, it is admitted that shearing actions bring about the appearance of cartilage in the connective tissue on which they are exercised repeatedly. They do not play any part in the formation of bone tissue.

III. THE DEEPER MECHANISM OF THE ACTION OF MECHANICAL FACTORS

Though the influence of the mechanical factors on the general morphology of bone tissue is well established, we know, on the contrary, almost nothing of the exact mechanism of this influence. It is difficult to state the problem, and in short it but gives us an idea of our ignorance.

Mechanical actions, especially pressure and traction, can act on the cells, the fibrils, the pre-osseous substance, calcification, and the vascularization of bone.

Influence on the Cells.—Conformable to the general histological views, it is by action on the bone cells, the osteoblasts and fibroblasts, that the mechanical influence on bone has usually been explained. W. Roux, in his general theory of the mechanics of development, admitted that functional excitation brings on an augmentation of the cellular functions. Applied to the influence of mechanical action on bone, this conception brings into play a trophic action of the mechanical influence on the cells: functional hypertrophy or atrophy by inactivity.

Undoubtedly in parts of his explanations, the theory of W. Roux is more open to criticism, especially when it attempts to establish the mechanisms. The action of pressure on the bone cells in particular should be elucidated.

In short, with a bearing a little more precise, the conception of Roux goes scarcely further in the determination

of mechanisms than the vague opinion, admitted up to his time by all biologists, that "function supports nutrition."

Influence on the Fibrils.—The action of traction is predominant on the determination of the arrangement of the fibrils and on their number.

It is through acting on them that morphogenetic action especially exercises itself.

The mechanism of this influence is of a physicochemical order. It is still little known, but one gains the impression that it probably acts by orienting the filaments in the exact direction of the lines of traction or pressure. It is a process of orientation of the colloidal particles, such as are known in a series of colloids, for example in India rubber.

Influence on the Deposition of Pre-osseous Substance.—The deposition of the pre-osseous substance amounts to an increase in the viscosity of the fundamental cementing substance, with impregnation with special products, probably mucoids.

This physicochemical phenomenon is dominated by mechanical influences. One understands then that the latter, in harmony with chemical action, can intervene in the laying down of pre-osseous materials.

Unfortunately, this is only an hypothesis. No precise fact has as yet been brought out on this question.

Influence on Deposit of Calcium.—As we have already shown, in Chapter III, mechanical influences can affect the deposit of calcareous material in the pre-osseous matrix.

This deposition implies the putting into play, among other things, of processes of diffusion and absorption. These processes can be modified by the intervention of mechanical influences. Diffusion into a mass of gelatine is not the same according as the block is or is not submitted to compression.

It is the same way with the phenomena of absorption. But here again, these are but broad general ideas, rather than precise facts.

Influence on Circulatory Conditions.—General circulatory conditions play an essential rôle in the metabolism of bone tissue, its growth, preservation, or resorption. They influence the local humoral actions which are so important.

Now, it is very probable that pressure and traction are not without a part in the circulatory regimen in a region where they are in play. A complete series of researches should be undertaken in this direction.

IV. LIMITS OF MORPHOGENETIC ACTION HEREDITARY INFLUENCES

We touch here a very important question from the standpoint of general biology and physiology. Are external mechanical actions alone responsible for the general forms of bone, or should one admit the intervention of an hereditary process?

In the opinion of W. Roux, the congenital element, so to speak, of the form and structure of bone is non-existent. All arise through external effects exercised in the course of development.

A rather lively reaction has arisen since the first works of Roux. It has been thought that he had generalized a little too quickly. It seems probable that an important congenital model of bone form and structure exists. Gebhardt, Braus, and more recently Weidenreich, have admitted that the general form of the embryonic model of a bone plays an indisputable part. Numerous works have been devoted to this question. It is impossible for us to enter into their details. We will content ourselves with noting the very typical example given by a pupil of Braus, Keck. It consists of a malformation of a lower extremity observed in an infant four weeks of age. The tibia was isolated, surrounded only by a tegumentary covering. No fundamental mechanical action could have affected it. Nevertheless, this tibia had its usual shape, and this proves

it independent of external actions. It lacked only the sculpturing of the bone surface. The latter: processes, ridges, etc., are hence exclusively of functional origin. But this is not the same thing as the general form of bone, which is fixed by heredity.

The difficulty is in fixing the boundary between that which is congenital and that which is of functional origin.

In a general way, one can remember that those things which are acquired under the influence of functional excita-

Fig. 12.—Malformation of the lower extremity of a six-weeks-old infant (Keck's case). Tibia with its usual general form, in spite of the absence of all morphogenetic action.

tion are in the form of details, the processes, etc. But the general disposition of bone is determined by development. Actual forces only serve to modify a comprehensive form imposed by the development of the embryonic outlines.

We shall content ourselves by noting these facts and problems, referring the reader, for further details, to the fundamental works of Braus, Weidenreich, and the recent monograph of W. Müller.

CHAPTER VI

THE PERIOSTEUM

Debated with acrimony for nearly two centuries, the question of the periosteum still remains unsettled, each school of thought keeping on the subject an absolutely uncompromising attitude. The controversies have brought out a mass of very interesting work which has still further complicated matters.

The researches which we have pursued for several years give, we believe, the solution of the problem. It is to be noted that they have led us to hold an opinion which is the exact opposite of the one which we held in the beginning. Originally convinced of the specific osteogenetic rôle of the periosteum, we today consider the latter as a functionally commonplace membrane.

We suppose the history of the periosteum is known. Ollier and more recently Hey Groves have set it forth in a complete way. We refer to their works for all that which is historical, and we will only speak in such a way as is necessary to actually understand the phenomena which take place in it.

I. STRUCTURE OF THE PERIOSTEUM

It is necessary to give up exact histological ideas.

The periosteum is the fibrous membrane which surrounds bones and separates them from the environing tissue: it is nothing more. Its morphology is not everywhere identical. At those points where muscular fibers are inserted on bone, its fibrous organization is very different from that which one meets with at the point where bone is situated beneath a mucous membrane or beneath the skin. There are re-

gions where there is absolutely no periosteum, muscular fibers inserting themselves directly on bone: for instance the linea aspera of the femur. This anatomical detail has been little appreciated. It is, however, of a nature to cause suspicion as to the osteogenic function of the periosteum.

A. Normal Periosteum

In the adult it is made up of solid connective tissue bundles. It is the result of a periosseous condensation of connective tissue, caused by the tissues being forced back upon themselves at the point where the bone is free. It is sharply isolable.

One can consider it as being composed of two layers: an external adventitia layer, made up of loose connective tissue, and an internal layer made up of solid fibrous bundles and elastic fibers. The fibrous bundles are for the most part parallel to the long axis of the bone. There are fusiform connective tissue cells, located between the bundles.

The elastic fibers are abundant in the periosteum. We do not know why.

The internal layer adheres directly to the bone, without the interposition of any cellular layer whatsoever. The degree of adherence is variable at different points: it depends upon the presence of oblique fibers inserted both in the bone and in the periosteum. These fibers constitute a means of union of an extreme solidity. The degree of adherence between bone and periosteum is a function of the quantity and solidity of these osteoperiosteal fibers.*

When the periosteum is composed of longitudinal fibrous bundles, the fibers of union are relatively few in number.

On the other hand, at the points where the muscular fibers are inserted directly on bone, the periosteum disappears at the points of the osteomuscular junction.

Is there anything else in the periosteum?

Classical treatises speak, always inexactly, however, of

an internal layer of embryonic character, situated, just in contact with the bone, which would be dormant in the adult, all the time remaining susceptible to a reawakening under the influence of irritation. In reality, this layer does not exist.*

There are, on the deeper aspect of this membrane, between the fibro-elastic layer and the bone, only rare capillary vessels which reach the Haversian canals, but there is no special cell.

The periosteum in the fetus and in the infant is constituted by a layer of young connective tissue, embryonic, as are at this period the tendons and ligaments. On its deep face there are found layers of young bone.

In the older fetus and in infants the fibrous layer is always better differentiated, less, however, at the exact point of contact with the bone than a few millimeters further away from it. It contains numerous capillary vessels, the fibrous elements are less evolved, and the connective tissue cells are of a young type.

Medullary spaces which open on the surface of the bone are continuous with the connective tissue spaces, and there is no interruption between the connective tissue of the Haversian canals and that of the periosteum.

It is to this layer, scarcely differentiated, that is attributed a specific osteogenic rôle which gives it the name of "osteogenic layer" (Ollier), "sub-periosteal blastema" (Ollier), "subperiosteal marrow" (Ranvier), etc.

It is impossible to find in these cells cytological characters which allow of their being distinguished from those

*The osteoperiosteal fibers referred to above are the fibers of Sharpey. It should be noted here, however, that I believe that the internal layer, the existence of which is denied by the authors, can be demonstrated in histological preparations of almost any bone and especially well in the bones of young animals. In the typical periosteum covering long bone there is an inner layer of rather loose reticular connective tissue which lies between the dense fibrous layer and the bone. This layer contains small blood vessels, wandering cells, rather young connective tissue cells, and a variable number of osteoblasts which are usually applied to the bone. The loose connective tissue of this so-called cambium layer is continuous with that of the Volkmann's canals which perforate the cortex and communicate with Haversian canals.—*J. A. K.*

of the connective tissue. Heitz-Boyer and Scheikewitch, like ourselves, have shown this in their studies in the war.

B. The Irritated Periosteum

This is the classical term. In the mind of surgeons, it has a definite meaning; physiologically it has none. It would be well for this ill chosen expression to disappear from surgical language. It is a term of metaphysical character: irritation is a state of mind and not a state of tissue. What is called irritated periosteum is a congested periosteum modified by traumatism or infection.

Here there is reason to examine the histological state of the periosteum so changed, since experience shows that it forms bone. It was formerly said that, under the influence of irritation, the fibrous tissue of the periosteum reverted to its embryonic state. Its capillary vessels, infrequent in the normal state, were increased. The connective tissue took on the character of granulation tissue which was developed between the fibrous bundles in the edematous matrix. The periosteum, infiltrated, swollen, and edematous, became thick, and of a lardaceous, chondroid consistency, causing the earlier authors to believe that cartilage was formed in periosteum and that this period constituted the cartilaginous stage which was considered necessary for bone evolution.

In like manner, the connective tissue cells increased in volume and showed signs of activity which were wrongly interpreted as symptoms of a secretory agency.

In reality, when one examines, without preconceived ideas, the periosteum in this phase, one has the impression that it is transformed into granulation tissue, or if one prefers, that it returns to the embryonic state. It has then all the characteristics which we have assigned to the ossifiable medium.

C. Blood Vessels and Nerves of the Periosteum

The periosteum is the passageway for vessels going to the bone. Of little importance in the adult, they are slightly more developed in the fetus. There is continuity between the capillary loops of the periosteum and the capillaries of the connective tissue spaces in the Haversian canals. The circulation of the outer layers of bone is continuous with that of the periosteum. When one separates the latter from the bone surface, one constantly finds a disturbance of the nutrition of the outer layers of bone. But these exchanges are very rudimentary in the adult. The circulation proper of the bone is assured by the nutrient artery.

The periosteum contains nerves which are still almost unknown from the histological point of view, and are of a very obscure significance. One cannot well conceive what could be their rôle in this fibrous membrane with such a singularly limited physiological activity.

It is probable that these nerve extensions are related to the muscle sense (sense of attitude or of equilibrium). They are appendages of the muscular, rather than of the skeletal system. They also certainly regulate the local vasomotor function.

II. THE ROLE OF PERIOSTEUM IN OSTEOGENESIS

Since the time of Du Hamel, a connection between the periosteum and bone regeneration has been believed to exist. It would be the specific organ of osteogenesis: periosteum would fabricate bone just as the germinating layer of the epidermis constructs the strata of the latter, just as the cambium layer forms wood.

In spite of the old objections and contradictory experiments of Goodsir, Sedillot, Marmy, Macewen, etc., this is still the current opinion among surgeons, although war surgery has singularly modified ideas on this point (Heitz-

Fig. 13.—Radiographs of a few of Ollier's experimental specimens from the Musee Ollier at Lyon. *1*, Ossification in detached periosteum, tibia of dog (series 12, 1864). *2*, Ossification of a rolled strip of periosteum (rabbit; No. 2, 1862-64). *3*, Ossification of a rolled periosteal strip (rabbit; Series 15, 1862). *4*, Ossification of a rolled strip of periosteum (rabbit; Series 16, 1863). All these operations were done under septic conditions.

Boyer). Personally, at the beginning of our joint work (1915), we considered this a true expression of what actually occurs. Brought up in the traditions of Ollier, we had been taught to consider this dogma as one of the most firmly grounded in surgical physiology. We had no idea, knowing the experimental works of Ollier, that it would be useful to reopen the question. Our first researches were inspired directly by the classical teaching and established more firmly the technical value of the principles which he had stated. But as soon as we had met with the details of the phenomenon, it seemed evident to us that if the facts brought forward by Ollier were absolutely unassailable, the interpretation which he had given them were to be rejected entirely. Ollier was not a histologist—they were rare in his time. He rarely used the microscope and never at first hand. What he thought he had seen fitted in with the facts he observed macroscopically and justified the technic on which his entire work rests. It was natural that the intimate details of the phenomenon escaped him.

It is moreover to be noted that in the beginning Ollier had had the idea that the periosteum was of no use. He was at first very much surprised to obtain experimentally results contrary to those he had anticipated. But when one considers the philosophy of his work, one is convinced that it is due entirely to the surprising result of experiments which should have given reversed results. Anyone who has seen his specimens of ossification of fragments of periosteum, wrapped around muscles, understands very well the suddenness of the conversion which took place in this great biological mind, which followed the religion of facts.

A. The Periosteum as an Ossifiable Medium

When the periosteum is "irritated," and we have seen above the meaning of this word, it assumes the character of granulation tissue, that is to say, it becomes young con-

nective tissue, slightly differentiated, for this reason subject to ossification. But let us not forget that all tissue of the connective tissue type, in identical conditions, is

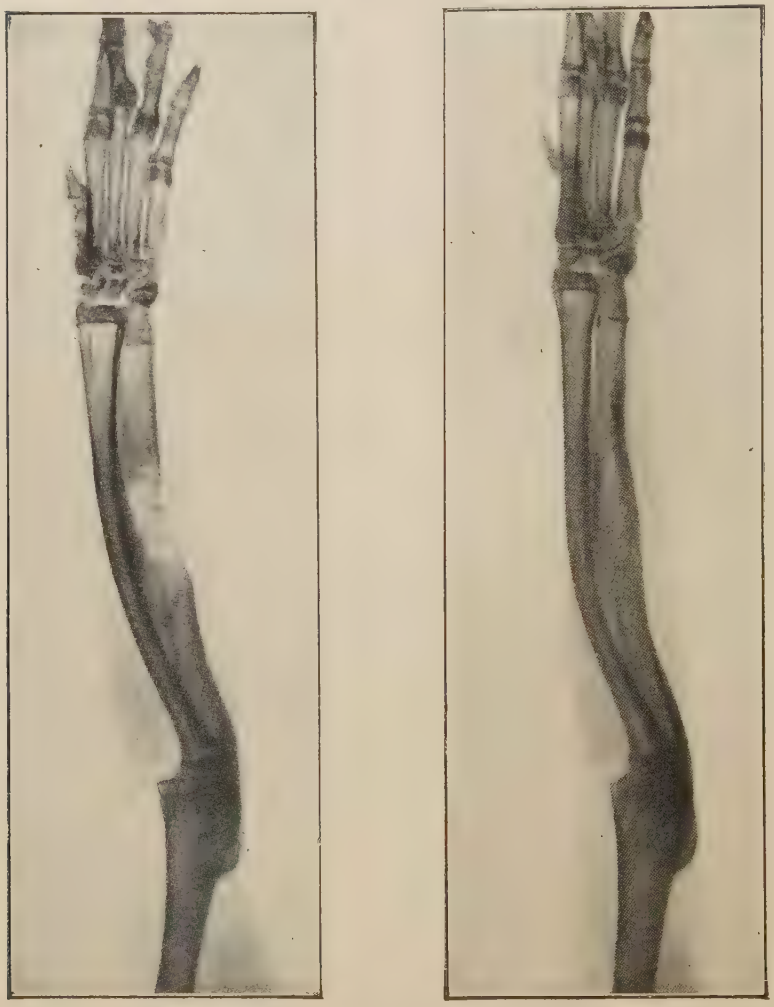

Fig. 14.—The effect of preserving the bone débris in subperiosteal resection. On the left, subperiosteal resection of the left ulna without preservation of chips of bone in an adult rabbit. Condition 82 days following the operation. There is no bone reconstruction. On the right, the same operation with preservation of bone chips, in an adult rabbit. Condition 69 days following the operation. Complete bone reconstruction. (Personal experiments done with J. Haour.)

susceptible to the same evolution and may become a good medium for bone metaplasia.

This peculiarity that the periosteum presents is that *this*

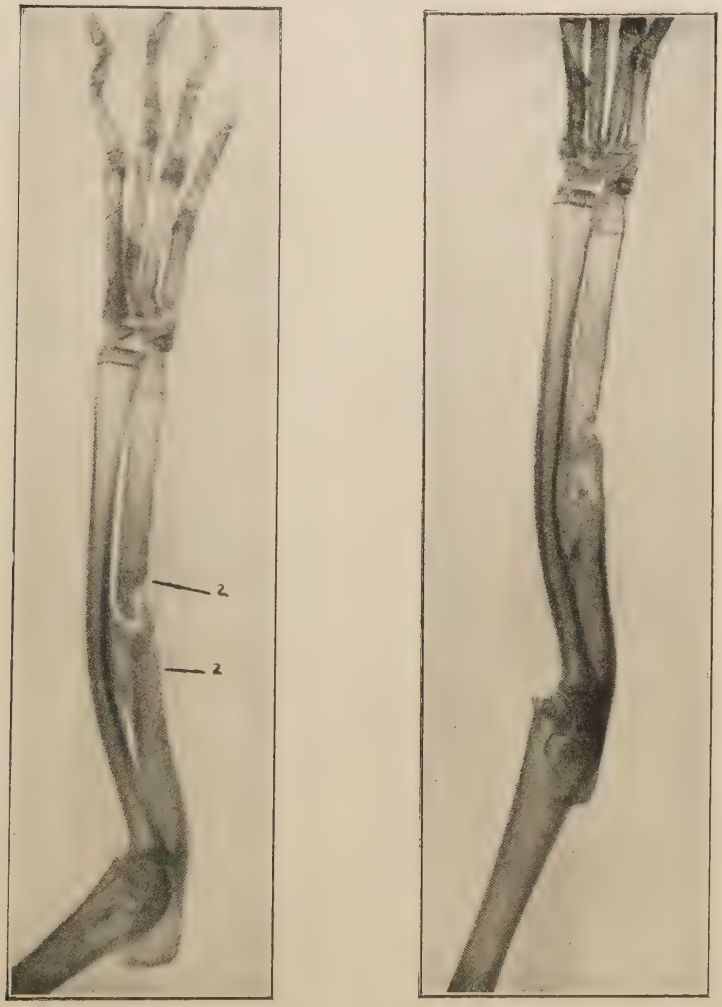

Fig. 15.—Aseptic subperiosteal resection of a centimeter of the left ulnar diaphysis. Insufficient preservation of bone chips at operation site. Operation technically incomplete because of the condition of the bone which appeared very fragile, hence the unsatisfactory repair at the end of 28 days. Rabbit very old. On the left, 28 days after operation. On the right, 107 days afterward. (Personal experiments.)

return to the embryonic state takes place in the exact vicinity of bone tissue. Because of the circulatory continuity of the periosteum and the outer layers of the bone, every irritation of one reacts on the other. Consequently the reversion of the adult periosteum to the embryonic state coincides with a hyperemia of the outer bone layers, and the latter determines a resorption which is translated into an enlargement of the Haversian canals. These phenomena occur simultaneously and are indissolubly connected. But the free resorption of phosphocalcific material creates a local calcium excess, the essential element of osteogenesis.

Ossifiable connective tissue medium implies calcareous material; the two conditions of ossification would thus take place in the periosteum under the single influence of congestion. New bone is automatically formed without the intervention of a specific mechanism.

An area of ready ossification, the periosteum is not a specific organ of osteogenesis. Experiments with subperiosteal bone resections and of periosteal transplantation, on which the classical doctrines rest, brings out as clear a proof of this as one could desire.

One sees here that the periosteum alone, without bone flecks on its inner aspect, is not ossified. If it is detached close to the bone, with bone particles on its deeper aspect, the fragment ossifies. It is from this point of view that Ollier had unheard-of good fortune in accidentally finding what he was not expecting. If circumstances had caused him to take a blunt instrument, his fundamental experiment would have given entirely different results, and bone surgery would have been directed in an entirely different direction.

Consequently, the results obtained by Ollier are unassailable. In perfecting the technic of Ollier, which will be taken up later on page 121, one can certainly, with adult periosteum, without previous preparation, without "pre-

liminary irritation," obtain an aseptic intraperiosteal regeneration such as Ollier never knew. But from a biological point of view, these results cannot be interpreted as Ollier believed.

B. Experiments on the Periosteum

We have repeated, both on man and on animals, with J. Haour, all of the classical experiments, and the following is what we have observed.

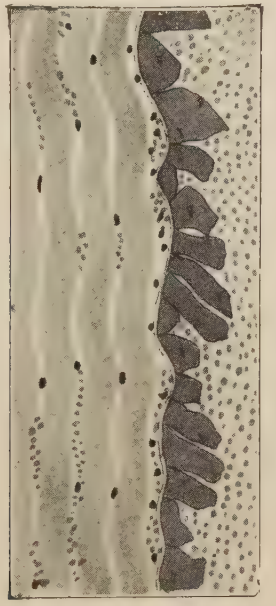

Fig. 16.—Diagram of periosteum detached by instrumentation. Presence of bone flakes adherent to the periosteum, and in contact with an effusion of blood.

The simplest experiment consists in slightly elevating the periosteum from the underlying bone. Bone grows beneath the periosteum, giving a kind of exostosis. What has happened? The periosteal stripping has caused, along with capillary rupture, a subperiosteal hemorrhage, a return to the embryonic state of the periosteum. There is

organized at that point a proliferating connective tissue and therefore an ossifiable medium. On the other hand, the hyperemic outer bone layers undergo resorption. At the end of from five to eight days, in the new connective tissues at the exact point of bone contact, bone trabeculae appear. Their formation continues gradually from the bone to the periosteum, but it constantly makes its appearance from the surface of the bone.

Fig. 17.—Diagram of the transformations undergone by detached periosteum (eighth to tenth day). Edema, connective tissue organization of the effusion.

This is easily observed histologically in serial sections. The first bone elements are not born of the stripped periosteum, but from the bone, and they originate in the embryonic connective tissue which results from the organiza- of the clot in contact with the bone. This fact, noted first in 1836 by Miescher, and often rediscovered since then, has appeared, generally, to be little in harmony with classical explanation. (See Figs. 18 and 22.)

If one loosens with a sharp periosteal elevator a periosteal strip, of the length of a diaphysis, and if one wraps this pedunculated strip about the muscles of the leg, for example, or if one encloses it in an intermuscular space, fixing it so that it may not retract too much, one obtains, according to the case, either a simple fibrous band or a fine bone ring. (See Fig. 20.)

Fig. 18.—Diagram of new bone formation in roughened periosteum. New bone appears around the old which dies and finally disappears completely. Compare these illustrations with those published in Volume I of the *Treatise of Reconstruction Surgery,* page 152.

When the experiment gives a positive result, it is so plain that one understands Ollier's change of belief. But, the results, always positive for Ollier, have been constantly negative in the hands of others. It is even so in our day: according to the experimenter, the result is or is not positive. We have repeated the experiments and obtained at will bands without ossification and ossified bands in the

form of rings. In the rabbit we have obtained rings a centimeter and a half long, visible on the twentieth day, visible radiographically (Fig. 20), and found again six months later at autopsy. The variable results are only a question of technic, apparently insignificant, but in reality essential.

Preoccupied with keeping the precious osteogenic membrane intact, with extreme care Ollier stripped the periosteum of rabbits and dogs (a difficult operation at best), using a very sharp periosteal elevator and never losing contact with the surface of the bone. In doing this, he removed, at first without desiring it and later intentionally, little bone plates on the surface of the diaphysis which remained adherent to the deeper aspect of the periosteum. These flakes, he said, were there to protect the osteogenic layer from the slips of the instruments. Under these conditions he always had positive results: when one operates as he did, the same results are always obtained.

Several of his contemporaries, less careful and not governed by a theoretical idea, operated differently. They stripped the periosteum by pulling and prizing the bone with any sort of instrument, the blunt point being applied against the periosteum. In these conditions the periosteum is stripped off without carrying away any of the bone with it. The experiment, apparently identical with that of Ollier, is in reality very different. The results were always negative. Ollier explained these failures by saying that the osteogenic layer in these latter experiments had remained adherent to the bone, and that consequently the stripped periosteum was sterile. The explanation was erroneous, since the osteogenic layer does not exist. But obviously it was the technic which accounts for the results.

Osteogenesis, in the experiments of Ollier, is due to the fact that he detached, with the periosteum, the ossifiable medium, bone, or calcific material, susceptible of resorp-

tion. If one operates differently from Ollier, one detaches only an ossifiable medium which, when not utilized, regresses and becomes a simple fibrous band. In the last analysis, Ollier, as well as his opponents, was right. The periosteum of the dogs of Macewen did not have qualities different from those of the dogs of Lyons. But the technic at Lyons and at Glasgow was different. The results are self-explanatory.

The subperiosteal resection of a diaphysis gives exactly the same divergent results according to the technic employed. If one detaches the periosteum with the bistoury and traction, the resection is not followed by any regeneration, even at the end of ten months, while if one detaches carefully with a sharp periosteal elevator, in the manner of Ollier, the periosteum of the zone which one wishes to remove, the diaphysis is rapidly regenerated in the periosteal shell. The result is better than that obtained by Ollier and the regeneration is, so to speak, ideal, if one takes care to reconstruct with suture the periosteal mould of the new bone. Under these conditions, in a month, the diaphyseal continuity is reestablished and soon the form is integrally recovered. (See Figs. 14 and 15.) The explanation of these results is always the same.

A general statement should be made. In all experiments made on small animals, rabbits, cats, guinea pigs, chickens, small dogs, there is a whole mass of causes of error and technical difficulties, due to the smallness of the bones and the thinness of the walls of the diaphyses and their friability. It is extremely difficult, for example, to make a diaphyseal section without producing fissures and bone shattering. On account of this fact, a considerable number of experiments which are relied on have in reality no sort of value whatever. It is this which accounts for the enormous superiority of human specimens. If the periosteum truly possesses the property of fabricating bone, a fragment of periosteum completely detached and transplanted in any

given point in the economy should be capable of producing bone. The experiment suggests itself. It has been done from the beginning of these researches, and since then it has

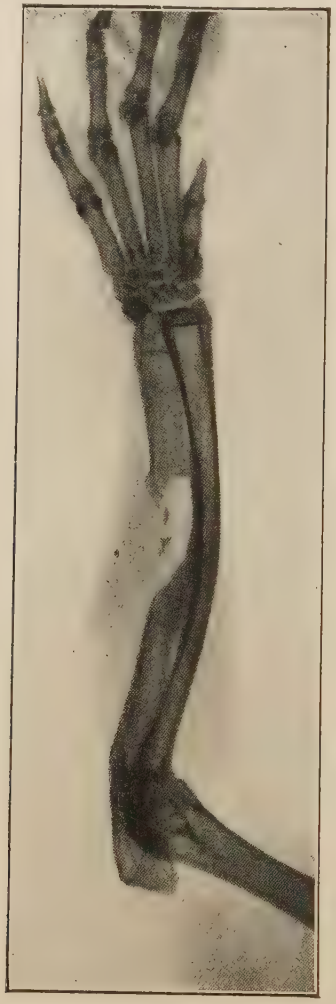

Fig. 19.—Aseptic extraperiosteal resection of a centimeter of the right ulnar diaphysis in a rabbit. The loss of substance is replaced by a segment of human vein filled with coagulated blood. Fragments of bone disseminated about this fragment. Result sixty-three days after the operation. No ossification whatever. The bone particles are not resorbed, the vein has become a hard fibrous cord. Ultimately the radius fractured after slow absorption, because of the loss of substance. (Personal experiment.)

been attempted in multiple ways. Ollier had the good fortune to obtain a few fine successes. But they must have been few in number, for in his museum one finds only two specimens of it, both of which figure in the *Treatise on*

Fig. 20.—Detachment of a strip of tibial periosteum with a rasp in an adult rabbit. Bone particles on the deeper aspect of the strip. This is wrapped about the muscles of the leg. Fixation to the deep aponeurosis. Radiograph at the sixty-first day. (Personal experiment.)

Regeneration. It is difficult to believe that from 1856 to 1900 the experiment had never been repeated by him. In reality, the results are practically constantly negative. Personally, we have never been successful.

But, on the other hand, Ollier twice had incontestably positive results, of which one, in a cock's comb, is particularly impressive.

With the classical conception these conflicting results are incomprehensible. They are very well explained, on the other hand, with the help of the mechanism which we develop. The negative results are due to the death of the fragment of grafted periosteum which does not return to the embryonic state and does not create an ossifiable medium. The successes are due to the fortuitous presence, on the deep aspect of the periosteum, of particles of bone intentionally or unintentionally detached.

One might think that we intend to say by that, that a kind of bone graft is sometimes made. Such is not our thought. All transplanted bone fragments die, resorb and, as always, it is uniquely in dying that bone gives rise to new bone.

In man, it is today well known that a periosteal graft alone is incapable of producing bone. If osteoperiosteal grafts are known to have the enormous success which they have achieved in contemporary times, one also knows that this is because of the fact that in making them one transports both the ossifiable medium and the calcareous material.

It is interesting to recall that scrapings of the internal surface of the periosteum have been deposited in muscle and beneath the skin. Ollier, the first to do this experiment, thought that in some way he was sowing osteoblasts. Once he obtained a positive result with the production of very small bone nodules. Pochhammer, with a suspension of periosteal scrapings injected in muscles,

saw, in 15 per cent of cases, also the formation of small bone nodules. Nahahara and Dilger have observed the same thing.

One cannot truly admit that in an emulsion of products of periosteal scraping there could really be living osteo-

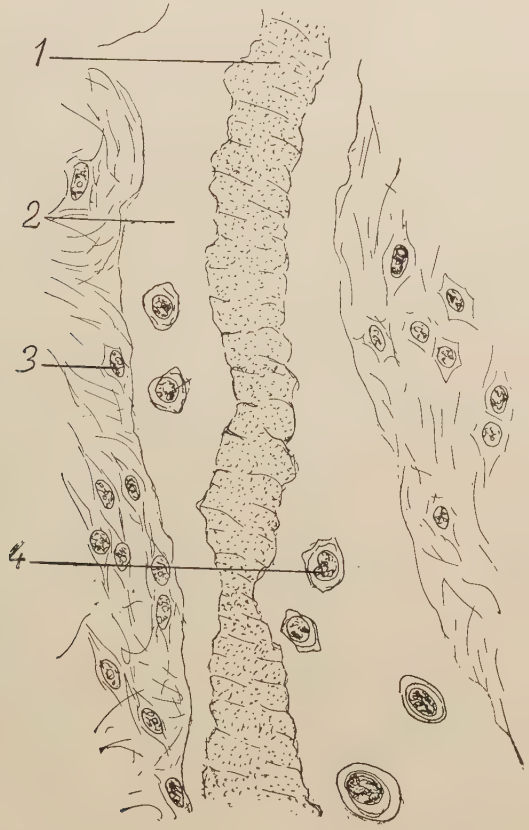

Fig. 21.—Newly formed bone *2* about the bone flakes from the rasp *1*. In *3*, osteoblasts; in *4*, bone cells.

blasts. That which one injects is microscopic bone debris which brings calcareous materials to the middle of the reactional granulation tissue which has been provoked by the injection.

Compared with that which we know today, these experiments are childish. One should reflect that Ollier made his periosteal emulsions *without asepsis.*

Fig. 22.—New bone in periosteum, 28 days after scraping according to the technic indicated on page 121. In the center of the new bone, flakes of bone are seen adherent to the periosteum.

One cannot likewise draw a valid conclusion from the experiments of Sultan, who enclosed particles of dead bone in the plications of living transplanted periosteum. He

thought he was bringing together a favorable irritation and bone material. New bone, when obtained under these conditions, is due to the presence of bone; the periosteum is therefore of no significance.

We should add that having repeated the experiments of transplanting fibrous periosteum, in placing on its deeper aspect powdered bone we have never seen ossification occur.

From another point of view Ollier, Grote and Morpurgo (99) thought to demonstrate that the periosteum of a cadaver, kept at about 0° during 168 hours, is capable, on grafting, of giving rise to bone.

We have not rejected these experiments, but we believe that all that is known of the vitality of tissue forbids one to accept that osteoblasts can thus stay alive for seven days. Today it is known that in detached tissues there is no latent life susceptible of some day resuming its normal rhythm: every ultimate appearance of life is due to a rehabilitation.

Experimentally, this point is indisputable, the only free transplants that are successful are those in which there are bone "seed" on the deeper face of the periosteum.

In the same way, in man, only those periosteal transplants which are lined with a layer of bone are truly capable of giving rise to bone. Following Ollier and Codivilla, Delagenière has shown, by numerous examples, the constancy of the results so obtained. It should be agreed from the constancy of these confirmatory results that they do not proceed from the periosteum.

It has been said that in these cases one truly grafts bone, and that the bone regeneration is a simple phenomenon of the culture of cells. But this is not exact. Histological proof shows that, in these conditions, the transplanted bone always dies. It is likely that scarcely any cells remain living in contact with the periosteal transplant, and it is in the latter, near the bone which has just died, as always, that bone appears.

Thus, contrary to classical opinion, we think that the periosteum has no specific osteogenic virtue whatever. It is only a site for ready ossification, for the simple reason of its juxta-osseous situation. But, any fibroconnective membrane close to a calcified or bony mass will possess the same properties. It should not arise in the mind of anyone to attribute to this membrane a specific osteogenic power. In relation to heterogeneous ossification, we shall have occasion to see numerous examples of these facts.

What, then, is the functional significance of the periosteum?

III. THE ROLE OF THE PERIOSTEUM IN RESTRAINING OSTEOGENESIS

Conforming to the old ideas of Havers and Bichat, the functional characteristic of periosteum appears to reside in the limitation of ossification. Fibrous tissue has, as we have seen, the property of arresting the extension of bone. When bone in process of formation meets with fasciculated or membranous structures, fibrous bundles, muscular bundles, or aponeuroses, across its path, it is arrested in a definite way. We have studied these facts in Chapter V and we shall encounter numerous examples of them in studying the repair of fractures and the formation of pseudarthroses.

In intraperiosteal osteogenesis the trabeculae are in general arranged perpendicularly to the surface of the bone. They develop in this direction. In time they come to press against the fibrous periosteal bundles which lie perpendicular to their line of progression. They can go no further, the periosteum has blocked osteogenesis. It has acted here as the thin epidermal layer acts in the cicatrization of wounds, blocking the growth of exuberant granulation tissue.

This function of limitation is not opposed to an osteogenetic function. Periosteum limits bone growth; but that

does not prevent it from becoming eminently favorable for the development of bone when, following circulatory changes, it has returned to a state of embryonic connective tissue, and also lies in close proximity to bone. These two phenomena have no relationship with each other.

CHAPTER VII

THE REPAIR OF FRACTURES

It is not our intention to give a complete study of the anatomy and pathological physiology of fractures. One will find here only a general view of the processes which are revealed at the site of fractures and which automatically lead to repair. These processes are not in themselves remarkable. They are the same as those studied in the preceding chapters. The formation of callus is not a phenomenon *sui generis*. It results from the interplay of a small number of simple agencies, the juxtaposition of which brings about conditions favorable for osteogenesis.

We shall begin by viewing the general progress of the process of repair of a fracture, then, in succeeding paragraphs, we shall return to the essential mechanisms of the phenomenon and to the variations which may be present.

We shall take up, as a type, the case of a simple aseptic fracture of a long bone and review the following points:

1. The general evolution of repair.
2. The nature and evolution of callus.
3. The late changes in callus.
4. The evolution of interfragmentary tissue.
5. General considerations.

I. GENERAL EVOLUTION OF THE PROCESS OF REPAIR IN FRACTURES

Immediately after trauma, the opening up of the site of a fracture permits one to observe, between the fragments, a clot, more or less important, which infiltrates the neighboring intercellular spaces: periosteum, muscle, and periosteal tissues. There are found cellular debris, fat droplets, etc. The extravasated blood coagulates rapidly

and spreads a fibrous mass around the fragments, which is occasionally adorned with the inexact and too ambitious name of fibrinous callus.

This fibrinous network is rapidly invaded by fibroblasts, which leads to its organization and transformation into embryonic connective tissue. This is the joining or connective tissue callus. This connective tissue organization of the clot is accompanied by a new formation of capillary vessels which penetrate it. In short, an embryonic connective tissue (granulation tissue) extends around the fragments. According to the violence of the trauma and the extent of the periosteal stripping, this infiltration extends a greater or lesser degree.

All of these phenomena are accompanied by a marked regional hyperemia. This is the same sequence of phenomena that follows all traumatism. It has here the usual consequences of active congestion: it brings the periosteum and neighboring connective tissue into an embryonic state. It affects the bone also. This hyperemia of the diaphyseal extremities has also rapid consequences; namely, the bringing about of a superficial bone resorption. The Haversian canals enlarge and the bone loses its density.

Between the fragments, if there is no displacement or if it has been reduced, there is a thin layer of clot. For a short distance (1-2 cm.) the medullary tissue is equally infiltrated with blood. The hematopoietic elements disappear more or less completely. There is a tendency to reversion to an indifferent connective tissue state.

In short, from this moment, all the conditions necessary for osteogenesis are present. A large ossifiable medium is formed, and in its vicinity resorbing bone frees calcareous elements; this is what we have called calcific surcharge. Trabeculae of young bone tissue soon appear at the angles of union of the periosteum with the diaphysis, very close to the bone, in the connective tissue organized in the old clot, and from there grow, little by little, until the two masses which they form unite with each other.

We have had occasion, during the war, to study in all stages the different steps in this process on a very great number of fractures. Profiting from the opportunity which we had of examining the same site daily, we were able to determine the precise moment at which ossification starts and the points at which it begins. We have never found bone before the sixth day. But from that time onward it was possible for us to see occasionally a granular and superficially worm-eaten appearance of the diaphysis (resorption), and at its connection there were seen very small granules of bone in the osteoperiosteal angle. Towards the ninth or tenth day we were able to encounter bone granules in the adjacent muscles (open fractures). The progression of the bone in the connective tissue mass always occurred very near to the bone surface, and the final stage of uniting bone callus, in the form of a spindle, was rather tardy.

Up to the thirtieth day, one does not generally find bone union just at the diaphyseal end-to-end contact. There are at times in contact with the hyperemic and rarefied bone very small areas of bone organization, but they are not unitive. Union of diaphyses is a slow phenomenon, which did not come about until the thirty-fifth day in closed leg fractures which we studied. This is not surprising. The exact conditions of interfragmentary ossifications are difficult to obtain, since they presuppose the fusion from one end to the other of the vascular-connective tissue contents of the Haversian canals.

II. DETAILS OF PHENOMENON. THE INITIAL FORMATION OF CALLUS. VARIETIES. EVOLUTION

It is important to return to these different stages. Each of them comprises a complex series of detailed mechanisms which are dealt with exactly.

A. Initial Fibrous Union

In the clot which surrounds the ends of the fractured bone, soft young fibrous connective tissue arises from all points about the fracture, especially from the Haversian canals, the marrow, properly speaking, and the periosteum.

This fibrous tissue organization takes place in the usual way. Concentric processes arise from the tissues enveloping the traumatic clot, and these meet one another in a length of time which varies according to the size of the hemorrhagic focus. When the latter is great, the fibrous penetration and organization requires more time. The ultimate formation of bone can be influenced by it.

In an unreduced fracture with very sharp fragments, it may happen that the serous exudate of the clot collects between the surrounding muscles, forming a sort of false cyst. The fibrin laid down on the intervening muscles prevents resorption. As fibrous tissue does not invade liquids, no peri- or interfragmentary organization is possible. Fibrous union cannot be accomplished and there is no possibility of bony union. We have made these observations in fractures of the thigh with great displacement.

Normally, the granulation tissue which invades and organizes the clot comes from all points of the focus. It is evidently more active where the wall is made up of young fibrous tissue; here it is more vascular and hence more active.

Ollier observed that the fibrous tissue filling the Haversian canals is the first to give rise to the granulations. This is only apparent. The granulation tissue exists everywhere in the margin of a fracture site, but in the case of the Haversian canals, the form of the granulations becomes much more apparent because it is thrown into relief by the dull white of the surrounding bone.

It is unnecessary to make the error of confusing effective existence of new-formed tissue with its naked-eye appearance in the form of granulations.

The marrow, properly speaking, does not participate in the fibrous organization and consequently in the ossification. This is readily explained because it is first necessary that the marrow give up its hematopoietic contents and return to a pure connective tissue state. When it happens to be fatty marrow, the reversion requires more time.

The ossifying rôle of the marrow has been much disputed. Bidder and Vincent have essayed to demonstrate an ossifying power which would intervene in the repair of fractures. We have reread with care the protocols of Vincent's experiments which were copied from those of Bidder. Only one is of value. He performed a transplantation of marrow into the comb of a cock, which gave rise to undoubted ossification. Much has been made of this experiment. It is well to note the following. The operation for taking the marrow which was to be grafted into the comb was made on a young chicken. The marrow was removed after resection of the diaphysis and opening of the medullary canal with scissors. In the view of those who have even once experimented on small animals, it is certain that one does not graft marrow alone. It is almost impossible to extract marrow which is free from bone trabeculae. It is the unsuspected presence of these bony particles, and to which Vincent naturally did not attach any importance, that accounted for the ossification in the comb.

Given the structure of the bone marrow, an organ of the hematopoietic system, it is impossible to admit that it has a specific power of ossification. One might as well grant that the spleen has such a power.

Moreover, when a fracture is properly reduced there is no callus in the medullary canal.

We have just viewed the insignificant part that the bone marrow has in the formation of the proliferating tissue which forms the clot.

Let us observe that of the periosteum.

From the moment that the periosteum is stripped, inter-

stitial hemorrhages and edema take place in it, because the circulatory conditions are upset. It is swollen and thickened (at times as much as 2 cm.), and is almost in a chondroid state. Histologically it reverts to the embryonic state and becomes the medium for fibrous tissue growth which pushes into the clot. It is always the same process, but with the differences imposed by structure.

When the stripping of the periosteum is nil, the fracture is reduced to a simple line, with preservation of the integrity of the periosteal envelope, and here the proliferation is obviously much reduced or nil, because the clot, which is the medium of connective tissue growth, is small.

In children, in whom fractures are so often subperiosteal, the great richness in vessels of the osteoperiosteal junction is the origin of a subperiosteal clot, hence there is in them a callus, which is more voluminous than in the adult with the same type of fracture, but this is essentially temporary.

When the escape of blood is little, the new-formed fibrous tissue is not abundant and the callus is small. Because the callus is small, certain writers have thought that the fibrin exerts a stimulating action on the production of callus. In reality, the explanation is much simpler. The small volume of the effusion causes the connective tissue callus to be very much reduced, and consequently also the bony callus which follows it.

It is in the same way that the slowness of consolidation in fractures by direct violence and after linear osteotomies is explained. Crushing of the tissue greatly restrains the effusion of blood, crushes the walls of the Haversian canals, and blocks them. The fracture, if one may use the term, remains a dry fracture. Fibrotic conditions are very unfavorable for the formation of callus. Thus is explained the known fact of the possibility of pseudarthrosis in these cases, especially when the fragments are in contact. There is added, furthermore, in

these cases another cause which embarrasses repair: it is the difficulty of rehabilitation and resorption of the bones. We shall return to this further on.

B. Rarefaction of the Fragments

Biologically the most essential phenomenon, though histologically unobtrusive, is constituted by the slow, but progressive resorption of bone at the extremities of the fracture.

Fig. 23.—Condition of the end of a bone fragment in a comminuted fracture of the tibia after 6 weeks. Exact replacement of the bony parts. *1*, Granulation tissue at the end of the fracture. *2*, Dead zone of the diaphysis; there is no bone rarefaction, no formation of new bone in the neighborhood. *3*, Zone in process of rarefaction. *4*, Production of new bone between the stripped fibrous periosteum and the surface of the bone. *5*, Fibrous periosteum.

This resorption is manifested by enlargement of the Haversian canals and of the connective tissue spaces. The bone disappears by osteolysis much less than by osteoclasis. This disappearance always precedes the formation of new bone tissue. One can therefore say that the genesis of new

bone trabeculae seems to be conditioned by the resorption of preexisting bone. Axhausen has admitted that necrosis of a portion of the bone ends prevents the formation of callus. Without knowledge of his researches, we reached a conclusion of the same type.

It is this which brought us to the conception of a local calcific surcharge, as the determinant of osteogenesis in a suitable fibrous medium.

This rarefaction had been noted accidentally for a long time. Ollier wondered at finding it instead of seeing in this area a productive osteitis. Bonome, Barth, etc., likewise noted it. Axhausen alone grasped its biological importance.

Bone rarefaction begins immediately after the trauma. It is produced only in the zone traumatized and throughout the extent of periosteal stripping.

It is this which changes the form of the bone ends and brings it to pass that, at about the end of a fortnight, they are no longer adaptable. All who have operated on fractures know that after the seventh or eighth day it often becomes difficult to obtain exact coaptation which is absolutely mathematical, and that the bones do not fit together as they do in the early days. That will suffice to show the importance of the rarefaction in the period preparatory to consolidation. The longer one waits, the more the phenomenon is apparent. Soon the laying down of new bone about the rarefied zones renders still more impossible an exact replacement.

Axhausen admitted that necrosis of bone is necessary in order that this end may be attained. In our opinion, that which comes into play is not, properly speaking, necrosis, which fixes bone in the state of a cadaver, but its rarefaction, which implies perfect vitality of the connective tissue fibrous contents of the Haversian canals.

The rarefaction proceeds with great regularity for a cer-

tain length of time, which one cannot fix. It is probable that it ceases when the circulatory conditions have returned to normal.

One notes it for quite a long time in certain radiographs, for it is necessary that the extremities of the fractured bones recalcify. The latter occurs only with the disappearance of the temporary peripheral callus and following an identical mechanism, but in an inverse sense, of the callus at the diaphyseal extremities. This is without doubt the reason why about eighty to a hundred days are neces-

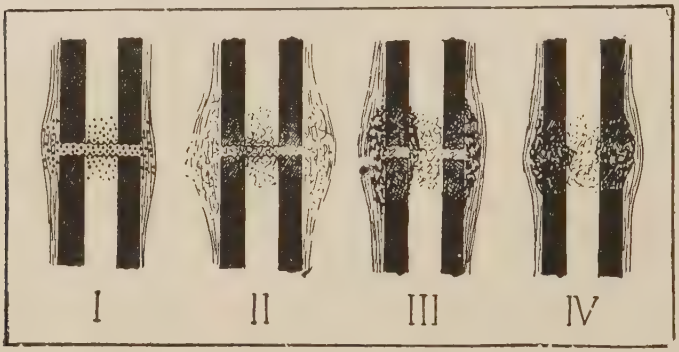

Fig. 24.—Diagram of the repair of a fracture. *I*, posttraumatic hemorrhage between the fragments and in the periosteum. *II*, organization of the clot, rarefaction of the ends of the fragments. *III*, formation of new bone in the clot organized in the periosteum. *IV*, union of fragments by callus.

sary for the rarefaction to appear arrested, when for a long time it has really ceased to progress. It is equally true, for that reason, that it is a long time before the radiographic image shows a column comparable to the original bone.

It is very curious to note that the callus for a very long time appears denser than the remainder of the diaphysis.*

*This is due to the fact that not only is the callus thicker than the adjacent bone, but also the marrow cavity is filled with calcified material, and considerable time must elapse before this can be absorbed and the marrow cavity reformed. Thus there is a greater volume of calcified material at the site of the fracture than in the adjacent bone.—*J. A. K.*

C. Formation of Bone Callus

In young fibrous tissue, formed as we have just seen, the bone trabeculae will appear suddenly.

They are first seen under the stripped periosteum, in its angle of junction with the bone. These early trabeculae are very delicate.

In a normal subject, the formation of bone tissue from primitive callus starts about the sixth day, but is not really very apparent until about the ninth or tenth day. In general at least twenty-five days are necessary for the formation of clinically firm callus. There are evidently very numerous variations according to the bones and the individuals. We are speaking here of minimal lapses of time.

In experimental studies, delays approximately identical for all animals have been observed. In the rat, Rigal and Vignal have observed that bone forms between the seventh and thirtieth days. From the thirtieth day onward the callus becomes compact and shows the customary modeling. These facts show that whatever the animal may be, bone requires the same length of time for its reproduction.

For this reason, one can say that immobilization of a fracture for thirty days is, if not absolutely necessary, at least very desirable.*

D. Extension of the Ossifiable Zone. Muscular Callus

We have already indicated that the muscles in the vicinity of a fracture often participate in the ecchymotic infiltration, in the edema and the periosteal modifications. From this fact, the ossifiable tissue is not always limited to the continuity of bone. It can extend beyond this. The

*Clinically the period of immobilization is much shorter in children than it is in adults, and it is shorter in cancellous bone than in dense bone and shorter in small bones than in large ones. Furthermore, the degree of the mobilization required is dependent upon the strain to which the part will be subjected and upon the tendency of the fragments to be displaced; and lastly, early mobility is believed to hasten bone repair and restoration of muscle power and joint motion. Consequently, we begin to move our fractured limbs as soon as we feel that we can do so with safety.—*J. A. K.*

extreme zone so modified can become ossified. Callus may project into muscle; this is *muscular callus.*

Recognition of the intramuscular development of callus is very old. With ordinary methods of clinical examination, intramuscular ossifications generally pass unperceived in an infiltrated and hard mass. It is considered rare. It is not as a rule shown by the x-rays. Furthermore, it is only temporary. However, direct examination shows its relative frequency.

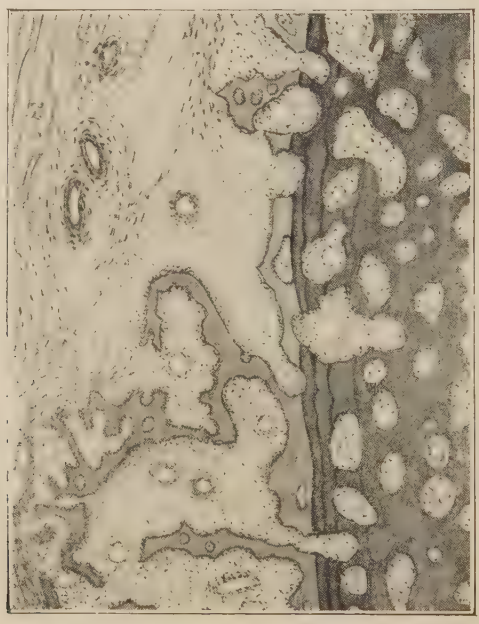

Fig. 25.—Formation of new bone on a rarefied diaphysis, with Haversian canals much enlarged. (Fracture of the femur by a war projectile.)

In fracture by projectiles the disposition of the parosteal callus is frequently curious. The focus of perifragmentary proliferation is often continuous with the proliferating tissue which occupies the path of the projectile. All of this path can ossify. Radiography may show a long bone splinter which inserts on the callus and extends through the length of the path of the projectile, an arrangement

which surprises and has given rise to the belief that there is a periosteal sowing by the projectile.

The formation of this parosteal callus has generally been the subject of extraordinary interpretations. They have even been explained on the basis of the presence of aberrant bone nodules.

Fig. 26.—New bone developed about a dead femoral diaphysis.

To what good purpose should metaphysical explanation be advanced when the real truth is so close at hand? Are not the connective tissue conditions the same as those present in the periosteum? Interstitial lymph currents naturally conduct there calcific materials arising from the seat of fracture. Cretin has found chemically an increase of the calcium in the muscles in the vicinity of fractured bones.

The presence of striated muscular fibers, enclosed in the bone tissue of callus demonstrates that this bone tissue is born of an evolution of muscle connective tissue itself, and not from the extension of a proliferating periosteal layer. If it were otherwise the muscle fibers would be pushed aside and not inclosed. It is this which allows the rejection of the old conception of Virchow and of Ranvier.

This muscle callus depends on the extent of the proliferating connective tissue. An attenuated infection, by favoring the formation of proliferating tissue, leads quite naturally to the formation of hypertrophic parosteal callus, and likewise to what are called mechanical irritations of the callus. By fracturing every ten days callus already formed, Ollier obtained at the end of forty to fifty days enormous ossifications. The experiment is easily carried out. In areas where immobilization is difficult, the ribs, for example, bone repair often goes beyond the limits of the periosteum and may reach the pleura over the intercostal muscles.

In this fibromuscular tissue brought to a state of granulating tissue, the multiplication of cells is very active; the fibroblasts are abundant and voluminous, with characteristic hypertrophy. The muscle callus shows in places a true sarcomatous tissue. One understands why in a classical work Cornil and Coudray should have taken the trouble to enumerate the differential histological characteristics of the exuberant muscular callus and osteosarcoma.

Like all peripheral callus, muscle callus regresses. Its bone trabeculae disappear through osteolysis. The embryonic connective tissue becomes fibrous again; the muscle fibers are brought together. This disappearance of muscle ossifications often takes place with extraordinary swiftness. In two or three days enormous masses may melt. Clinically the disappearance of the swelling and of the infiltration of the member are its apparent manifestations. But if one opens up a suitable site one is struck by the

dimension of the vessels and the intensity of the hemorrhages. This circulatory exaggeration is the actual cause of the disappearance of the bone trabeculae.

When the bone has disappeared, the muscles seem to revert to the former state. But perhaps this is only apparent. Researches in this direction would, without doubt, show the persistence of a muscle fibrosis. In any case, one may ask whether certain joint disabilities after fracture are not due to this very thing. The trouble does not lie in the articulation, but in the muscles which no longer allow stretching. After certain fractures of the thigh, one has the impression that the quadriceps having become inextensible, interferes with complete flexion of the knee.*

E. The Nature of Callus

The bone tissue of early callus is coarse. It is formed of a network of quite delicate trabeculae which delimit large connective tissue spaces filled with granulation tissue and lacking hematopoietic elements.

Its solidity is slight and it is very easy to break the interfragmentary union. It is also very easy to crush it by manipulation. Operations for vicious callus permit verification at any time of the properties of callus.

But when fractured, the primitive callus is repaired with great quickness and facility, by the formation of new hemorrhagic foci and of a new network of union. It would be commonplace to recall here that manual corrections of a fracture in vicious union are generally followed by a sudden solidification.

The slight density of the bone in callus accounts for its relative transparency to x-rays. Radioscopy can only show

*The reason that some of these knees cannot be flexed after fractures of the thigh is that the quadriceps muscle or tendon becomes adherent to the femur at the site of the fracture. On the other hand, a muscle which is permitted to remain in a shortened state or to contract without resistance for a long time undergoes a compensatory shortening without fibrosis as is beautifully illustrated in the contractures which develop in patients afflicted with infantile paralysis.—*J. A. K.*

repair which has occurred. Radiography itself gives only a very incomplete image of the callus. It is a constant finding that the latter should be much more voluminous than the rays indicate.

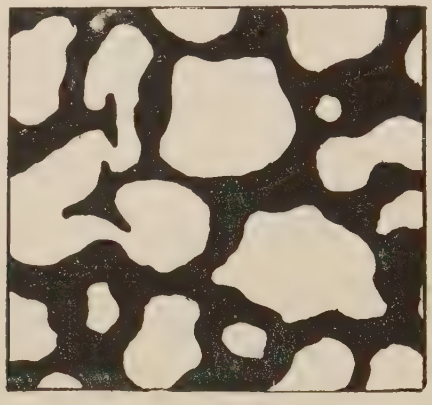

Fig. 27.—Silhouette of the bone trabeculae in callus (embryonic type of bone).

F. The Late Changes in Callus

Callus constitutes a rough means of union. The bony mass between the two fragments, badly delimited and voluminous, is of only mediocre solidity. Under the influence of morphogenetic agencies it will undergo a marked reduction in size. Its bone trabeculae arrange themselves in an orderly manner and increase in density and solidity.

This idea of the changes of callus is very old. Dupuytren taught that the peripheral callus disappeared entirely and that the true callus (definitive callus) formed between the fragments. In this he has a correct idea carried too far.

When a fracture has suppurated it is frequently the case that the new bone formed is of a mediocre quality. It never has, so to speak, a perfect architecture and a normal structure. It remains brittle and sometimes, at the time of the late change in the callus, a spontaneous fracture occurs. This, however, generally unites well.

This change of callus is dependent on mechanical forces to which the laws of morphogenesis apply.

III. ABNORMAL EVOLUTION OF FIBROUS CALLUS PSEUDARTHROSIS

Ossification is one of the possible means of the transformation of fibroconnective tissue callus, but it is not the only one; one may see its evolution into a fibrous or cartilaginous tissue.

A. Formation of Cartilage

At times one encounters in callus cartilaginous nodules or even extensive masses of cartilage. They constitute what is called cartilaginous callus, a bad expression, for these cartilaginous masses alone never weld fractured fragments. The cartilage only forms layers in the fibrous or bone callus.

Through a very rough analogy with the normal growth of bone, it has been believed for a long time—and many surgeons still believe—that bone callus necessarily arises from a cartilaginous callus. Fibrous phase, cartilaginous phase, bone phase, appeared to them to constitute the necessary steps in the building up of all bone, normal as well as pathological.

In the normal evolution of a bone there is nothing of this sort. Bone tissue always arises from connective tissue, even though the bone has a cartilaginous model as an antecedent. It is the same case with callus.

The mechanism of the genesis of cartilage is very simple. In the connective tissue callus, the fundamental ground substance, instead of ossifying, little by little takes on the character of cartilaginous material, a homogeneous and translucent aspect, as though it were congealed. Its cells become voluminous and round, and little by little, acquire the characteristic aspect of cartilaginous cells. This is a question of chondroid tissue, rather than of true hyaline cartilage.

The cartilage is never very homogeneous. It is composed of lobules separated by fibrous substance which is more or less vascular and sowed with bony spicules which arise irregularly and are isolated. At other times the cartilaginous formation is more extended and can involve the parosteal callus.

As a general rule the cartilaginous nodules are covered at their periphery by a thin bony layer. Between the cartilaginous center and the bone periphery the transition is insensible. There are no indications of the replacement of cartilage by bone through substitution. There are two intricate metaplasias present. Dead cartilage, such as is met with in epiphyseal cartilage, is nowwhere to be found.

Only a superficial examination of this callus can lead one to believe that there is a cartilaginous stage in the repair of fractures.

What then are the conditions which govern the formation of cartilage?

One is mechanical. Certain movements of tangential sliding and of little extent combined with inconsiderable pressure (shearing), experimentally bring about the appearance of cartilaginous metaplasia.

The researches of Rigal and Vignal, Kassowitz, Stubenrauch, Kapsammer, etc., have shown this. Fujinami, in his work on the repair of fractures in the different groups of animals, reported interesting examples of this; the application of immobilizing apparatus always prevented the development of cartilage. The repair of the fracture of the wing in birds takes place without or almost without cartilage; under such conditions, in short, these animals spontaneously immobilize their fractured member: the wing remains folded, makes no movement at all, and this is especially true when the ulna alone is fractured, because the radius then serves as a protective splint. Cartilage is more abundant in fractures of the humerus, because this is a bone which is difficult to immobilize.

Formerly Victorin Ollier found that when repeated daily massage was practiced on a callus in process of evolution, cartilage would appear.

It is this which Victorin Ollier, conforming to the view of his epoch, described in saying that massage prolonged the duration of the cartilaginous period. In reality it is the movement which causes the cartilage to appear. The frequency of the presence of cartilage in the course of the evolution of the callus in animals is to be ascribed to the fact that in them it is extremely difficult to immobilize the fragments of a fracture. Many experimenters have thought that in fracturing only one of the two bones of the forearm or the leg, the other making a splint, one could consider the immobilization as sufficient. In reality there are always movements of feeble amplitude arising from muscular contractions. And it is just because these movements are limited that they precipitate the cartilaginous metaplasia.

The general conditions of the humoral state are of equally great importance. It is this, in the experimental order, which corresponds to the influence of species. There are animals which form cartilage more readily than others: rabbits, mice, and birds. In the gray mouse, three days after fracture chondroid masses are already present. In man, this is exceptional and we have encountered it on only two occasions.

A humoral factor probably comes into play. All animals which readily form cartilage in the course of the repair of fractures (birds, mice, rabbits), are precisely those which form amyloid with great ease, and for relatively slight causes (mice: Finzi, Davidson; birds, rabbits; Wells). These two conditions: amyloid infiltration and chondroid infiltration, have histological and biochemical similarities. It is curious to compare them.

Generally the cartilage does not seem to persist. We are, however, poorly informed on this point, thanks to the

lack of direct observations. We have met with it on one occasion four months after fracture.

It has been freely admitted that, in certain unreduced fractures, the cartilage can become organized to the point of causing a pseudarthrosis (true new joint formation with cartilaginous covering). In reality, in our day, when one operates on pseudarthrosis more frequently than formerly, one never finds chondrosynovial pseudarthrosis. We have personally never met with it, and to our knowledge it has never been observed in the war pseudarthroses. The appearance of cartilage would perhaps be rather a secondary and late phenomenon. We have found it once in a fracture of the patella encircled for twelve years by a metallic wire.

What finally becomes of the cartilage? This can only be spoken of theoretically. We have no evidence whatever which permits the solving of this problem.

B. Blockage of Repair of Ossification by Fibrous Tissue. Fibrous Pseudarthroses

The connective tissue callus can undergo fibrous evolution. There results from this a pseudarthrosis.

Let us first examine the facts, after which we will examine the mechanism.

Observed Facts.—If the reduction is insufficient, the organization of the clot occurs along each fragment, but the two masses of young connective tissue which result from it remain separate. There is no interfragmentary connective tissue junction, hence no bone union. One finds simply a bony network at the ends of the diaphyses. The two fragments remain free, unless the free periosteal fragments lead to the fibrous organization and ossification which take place there, bringing about that which Ollier calls callus by periosteal criss-cross.

If, as one sees sometimes in great traumatisms with considerable displacement, there remains between the fragments which are more or less separated, a certain quantity

of serum, which in some way encysts the muscular masses which are covered with fibrin, the fibroconnective tissue products do not join and consolidation is just about impossible. We have had occasion to note this on operating on the fifteenth day a fractured thigh which continuous extension had not reduced. There was between the two fragments about three hundred cubic centimeters of yellow fluid enclosed by smooth walls, and the two diaphyseal ends, which were reddened, rarefied, and rounded, extended

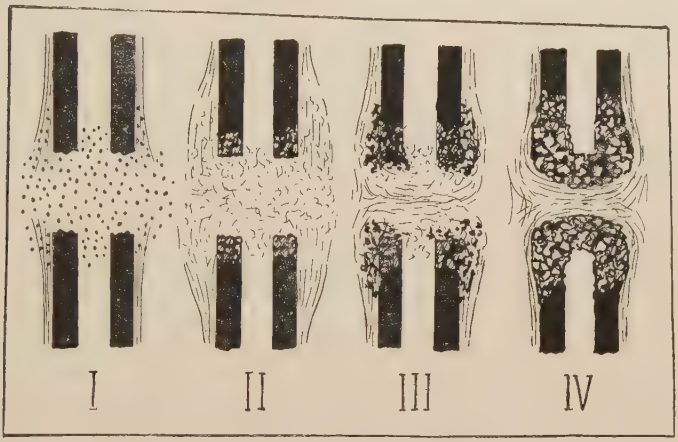

Fig. 28.—Diagram of the formation of a pseudarthrosis. *I,* post-traumatic hemorrhage, the fragments are very sharp. *II,* connective tissue organization of the interfragmentary clot and rarefaction of the fragments. *III,* new bone formation toward the ends of the fragments, fibrous transformation in the connective tissue callus. *IV,* the pseudarthrosis is formed.

into this liquid. It seemed to us that on account of this cyst consolidation was rendered impossible.

In other circumstances, hemorrhagic effusion being feeble, the periosteum lacking, and no utilizable fibrous investment being found in the vicinity, it was impossible that an ossifiable medium, properly speaking, could be formed. No connective tissue callus is created; consequently, interfragmentary ossification was impossible. There are two very characteristic examples of this: sub-

capital fracture of the femur and fractures of the skull. Each of these almost never unites.

In a third series of facts pseudarthrosis appears to result from a great or small interposition of muscle; this is the usual cause of closed pseudarthroses. One understands that, mechanically, it prevents all union. This is not because muscle cannot become ossified; the examples of muscle osteomas and parosteal callus occur to prove the contrary. But, as we have already said, ossification can only proceed in muscle in the longitudinal direction, that is, parallel to the fibers. When the latter are transversely placed, they constitute an obstacle which ossification cannot surmount. This explains the arrest of ossification which muscle interposition produces.

In other cases, pseudarthrosis follows infection at the seat of the fracture. Infection acts particularly by bringing about a sclerotic change in the connective tissue. It thus constitutes a mechanical obstacle which is more or less unsurmountable. Without doubt, a mild infection, by congesting and infiltrating with edema the parosteal connective tissue over a wide area, favors the formation of a voluminous callus. But when a certain intensity of infection, the limits of which it is impossible to define, is passed, tissue necrosis, prolonged suppuration, and the consecutive vascular alterations finally leave a fibrous connective tissue which is dense and unfavorable to ossification. Under these conditions ossification takes place only irregularly and insufficiently.

Suppuration, moreover, acts not only in this way, but one may suppose that it disturbs the local calcific changes. It can prevent them completely, either by carrying them away or by changing the calcareous materials themselves. More often, without doubt, it canalizes the callus in undesirable ways, and the calcific material thus carried away becomes the origin of those exuberant and disorderly ossif-

ications which form the curious irregularities about the diaphyseal extremities in pseudarthrosis.

But infection has still another harmful effect. Ossification, as we have seen, never takes place at the point where polynuclear neutrophiles are present. This is probably a matter of cellular digestion. Under these conditions, the bone deposit takes place only in spots and in an irregular fashion. It does not form a continuous callus.

In the fractures by war projectiles with a mechanism of which we have just spoken, there is added almost always the formation of a fibrous interfragmentary tissue, which encompasses macroscopic foreign bodies: débris of clothing, particles of wood, metallic or mineral powder, etc. The latter give rise to a dense sclerosis of the fibrous callus which blocks ossification.

One sees from the preceding how numerous are the local factors which can impede the formation of callus, in acting on the ossifiable matrix and in preventing the vascular-connective tissue junction of the fragments.

Mechanism.—In summing the matter up, in all of these facts three extremely simple phenomena come into play: the premature or tardy fibrous evolution of the ossifiable medium, which renders the connective tissue callus unutilizable for ossification, the action of blockage by the fibrous tissue which results from this, and the wasting through suppuration of the calcific material which arises from the rarefaction of the bone fragments.

Fibrous evolution of the interfragmentary connective tissue is absolutely fatal; however, normally, this is made less quickly than the bone growth. When the latter starts well, the connective tissue callus is formed before the bone tissue has birth. Then there is a race between the two antagonistic processes, ossification and fibrosis. Pseudarthrosis results from a more rapid progression of the fibrosis than of the ossification. It is the fibrosis which wins.

The problem of pseudarthrosis, in short, consists in accelerating the osteogenic and retarding the fibrous processes.

Consequences of the Formation of Pseudarthroses on Bone.—It remains for us to say a few words on the effects that the formation of a pseudarthrosis have on a bone and on the impossibility of consolidation. We have already seen that the hyperemia which follows traumatism has as a result the bringing about of bone resorption. We have said that, on the extremities of a fractured bone this active resorption goes on until the establishment of new circulatory conditions, that is to say, up to the time of consolidation or perhaps a little later than that. When union does

Fig. 29.—Change toward a common bone type by old compact bone after rarefaction (below the line *XX*) and of new bone of the callus (above the line *XX*).

not take place, resorption is prolonged well beyond the usual time and the rarefaction of the bone continues. It is said to atrophy. This term is biologically inexact. The truth is that the bones waste themselves on an impossible task, because without any circulatory change no new periosseous fibrous organization will take place.*

If there is suppuration, it often happens that the consequent fibrosis little by little brings the bone to an inverse circulatory regimen, resorption ceases and the diaphyseal ends condense, the last calcareous elements freed being utilized in the middle of the medullary canal, where the marrow is replaced by young connective tissue, and in the

*It seems to me that the rarefaction which takes place in the ends of the fragments at the site of a pseudarthrosis is due to atrophy of disuse. See note on page 207.—*J. A. K.*

contiguous Haversian canals. In this way, the two extremities of a bone in pseudarthrosis are formed of dense bone, hard and eburnated, which renders ultimate attempts at surgical repair uncertain, inasmuch as the formation of a callus and the taking of a graft require a well-vascularized bone and one permeable to the vascular granulation tissue of the union.

In other cases, and almost always when the fracture has not suppurated (closed pseudarthrosis), the bone remains rarefied, red, very weak, very vascular, continuing sluggishly its useless wear and tear for a long time. Only surgical restoration of the bony continuity can arrest this resorption. Technically, in such cases, this restoration by osteosynthesis or graft is made difficult on a bone which lacks solidity and crumbles at the least instrumental jar. But biologically, conditions are favorable to the formation of a callus, since the bone is in a state of resorption and because there the circulation is in a desirable condition.

IV. INFLUENCE OF THE GENERAL CONDITION ON THE REPAIR OF FRACTURES

The general condition of the subject has a considerable influence on the evolution of callus. This has always been known. Ollier showed that it was practically impossible to study callus in subjects dead of certain infectious diseases, particularly septicemia. Callus, in fact, disappears very quickly in the course of this disease. He recommended studying callus in subjects dead from violence without having had a long agonal period.

From this point of view the experiments of Fujinami are interesting. In studying the repair of fractures in tritons, one can see formation or resorption of callus according as one puts the animal on a full diet or fasting. The influence of nutrition on the repair of bone is of an extreme sharpness in experimentation. In the same way, the evolution

of fractures in cold-blooded animals, in the frog, for example, varies with the season; repair is very slow in winter and is rapid in summer (good nutrition).

In man, analogous facts have probably been observed in connection with the war privations of nutrition. We have not had occasion to read the special works on this subject. But the osteopathies of famine have presented facts of this order.

The influence of age, clinically clear, and still more so experimentally, arises, in part at least, from the question of nutrition. It is also possible that the special properties of connective tissue in young subjects play a part.

The mechanisms of the details of the influence of the general condition are numerous and are still little known.

Some of the more particular factors can nevertheless be indicated.

As ossification requires calcific materials, it is to the point to examine the rôle of general calcium metabolism. It does not seem to be of great importance. The richness of the blood calcium does not vary during the time in which a fracture is being repaired. The calcific phenomena which come into play seem to be purely local. The quantity of calcium necessary for the repair of a fracture is insignificant when contrasted with the calcific reserves that the organism possesses in the bones. When one notes the quantity of calcium that, usually without ill effect, a mother can withdraw from her skeleton to construct the bones of her child, one understands that fracture repair does not demand the putting into play of an extraordinary mechanism.

The part of the phosphorous compounds appears to be more important. In all ossification, the essential thing is less the quantity than the fixation of calcium. Now, the latter depends on phosphates. It is through the intermediary of phosphorus metabolism that the general state of the organism influences the repair of fracture.

The new facts acquired through the study of rickets have

established that all ossification, in order that it may take place in a healthy condition, requires a precise proportion of calcium and phosphorus in the diet and in the blood. When this relationship is disturbed, absence, delay, or anomalies of repair occur. Peterson has studied these data in the dog. By bringing about modifications of the phosphorus calcium relationship of the blood, he has prevented all repair of fractures which would normally unite in a month.

The influence of light is unquestionable. Percy noticed, it is said, in the course of the Napoleonic wars, that the cases of fractures hospitalized in churches united normally when they were placed on the sunny side, and did not unite when they were on the shady side. In contemporary times, this influence has again been noted. Personally, we have seen that heliotherapy has a manifest action on the repair of fractures. This is understood, since it brings about an intense hyperemia and thus aids the formation of the ossifiable medium and bone rarefaction.

Certain general pathological processes play a part in repair and are capable of giving particular qualities to the callus. It is known, for example, that fractures in rickets are repaired by very hard, dense callus.

A very large number of experiments have sought for the action of the endocrine glands. Clinically, the thyroid alone has a manifest action. It is known, thanks to Gauthier and Poncet, that certain delays in consolidation cease immediately after the administration of thyroid extract. For thirty years, thyroid medication in delayed union has shown, in certain cases, a very clear effect. It acts probably through the influence exercised by the thyroid hormone on the functioning of the connective tissue.

In castrated animals, in eunuchs, fractures are normally repaired. The genital glands do not seem to act on this particular direction of bone evolution. Marsiglia, in 1921, made a series of experiments without observing a single

modification in the evolution of experimental fractures. Moreover, since his time, neither thyroidectomy, hypophysectomy, nor ablation of the suprarenal have had any more influence than castration. It seems that the rôle of the endocrine glands is very limited in bone evolution.

Numerous works, which the experience of war surgery has amply verified, have shown that the section of the sensory and motor nerves has no action on the formation of callus.

Truth to tell, ossification is subject only to vasomotor action and, in this direction, one may say that the vegetative system alone is capable of influencing repair. In fact, in delayed union, even in pseudarthrosis, which neither musculofibrous interposition nor vicious reduction explains, periarterial sympathectomy has brought about rapid unions. This was first established by Kappis. We have verified it personally both experimentally and clinically. Callus is formed more quickly on the bone of a sympathectomized member than on the controlled bone of the opposite side. In man, in an old pseudarthrosis, evidently without interposition of tissue, we have found, ten days after the operation, a voluminous callus and the bones united.

V. GENERAL CONSIDERATIONS. CONCLUSIONS

Having reached the end of this long chapter on pathological physiology, it would be well to put the following question: Why is a fractured bone repaired?

In short, one must think that the repair of a fracture is not the consequence of an ensemble of operations, ordered with repair in view, that is to say, in view of a finality affecting the individual. All the phenomena which constitute it are blindly loosened by the traumatism itself and unfold themselves in a fatalistic manner, as in a flood.

There are in the beginning primary and simultaneous

biological events which are the immediate consequences of the traumatism: hemorrhage of the soft parts, rupture of bone, and paralytic vasodilation.

These phenomena in themselves cause elementary tissue changes, each unfolding itself individually, independently of one another, one might say, but soon having a mutual influence.

The hemorrhage is followed by coagulation. The clot forms. Embryonic connective tissue appears.

Paralytic vasodilation causes congestion. In the soft parts it produces edema. In the fractured bone it leads to bone resorption and the liberation on the spot of calcium salts.

From this time the general conditions of ossification are realized: the presence of an ossifiable medium and local calcium excess.

From that moment, under normal conditions, the formation of a callus is an inevitable automatic phenomenon. In fact, from the sixth to the tenth day bone appears.

Each of these phenomena is of itself commonplace. What is peculiar is their juxtaposition.

The essence of the process lies in a vascular congestion acting simultaneously on the connective tissue and a calcified tissue. In all this there is no regulation with regard to the functions of the skeleton. Therapeutics profits from a phenomenon which is not at all set in motion with a cure *in view*.

Heitz-Boyer developed, in 1918, a general theory, the histological basis of which resembled greatly our own observations, but the general conclusion of which seems inadmissible to us. According to him, all the phenomena of bone repair are essentially inflammatory and are connected with the existence of an aseptic or infectious osteitis which is at the same time rarefying and osteogenic. This osteitis liberates calcium salts from the old bone and these

liberated salts build up bone if they are in an area of development made up of inflammatory connective tissue.

There are two essential elements in all osteogenesis, but also unfortunately there exists a vexatious confusion between biology and pathology. Bone rarefaction, a normal phenomenon of bone life, or, more exactly, of its circulatory conditions, has nothing to do with osteitis or inflammation.

We see things differently and in a simpler way, it seems to us.

CHAPTER VIII

BONE TRANSPLANTATIONS

Under the form of aphorisms we once gave several definitions as to the meaning of the terms which every one uses in speaking of bone grafts.

It seems worth while to repeat these aphorisms here and to begin with definitions which are generally accepted.

One *transplants* living tissues (transplantation osseuse, bone transplantation, Knochenüberpflanzung, trapianto osseo).

One *inserts* dead tissue in living tissues.

A transplant which *continues to live* is a graft. There is a graft only when the continuity of the cellular life of the transplant is assured. A transplant which dies is not a graft. It is illogical to speak of dead grafts.

The transplant which does not live can be thrown off immediately as a foreign body, or tolerated, or slowly absorbed by the tissues of the host.

These definitions of terms are indispensable. In default of having these data, much time has been wasted in vain discussions, each one employing personal terms not having the same values as those used by his opponents.

The idea of the graft is very old, and its history has been frequently written. In fact, the subject begins with the works of Ollier, who was the first to bring out the biological question of the fate of the transplanted bone. He concluded from his researches that the transplanted bone dies and that the periosteum alone engrafts (lives).

From his time, it is unnecessary to stop except at the work of Barth (1893). He studied all the details of the biological phenomena and showed that if transplanted bone always dies, because of this fact it brings about the formation of new bone.

Since then the works on this subject have multiplied to such an extent that it is impossible to write its history in a useful way.

The exigencies of the treatment of war pseudarthroses have given new scope to researches on bone transplantations. From the enormous quantity of papers accumulated one can today draw quite a complete biological history of the phenomena which occur in a transplantation. Cunéo has recently given an excellent synthetic exposition of this process.

Leaving aside the question of surgical technic, we shall consider only the following questions:

1. The general evolution of bone transplants.
2. Death of transplanted bone.
3. Union and rehabilitation of the transplant.
4. Rarefaction and absorption of the transplant.
5. New bone formation.
6. Conditions necessary for the maintenance of the newly formed bone.
7. The transplantation of dead bone.
8. The rôle of the periosteum in the evolution of a transplant.

I. GENERAL EVOLUTION OF THE TRANSPLANT

In man, a fragment of bone transplanted into another bone always dies. At the present time this fact is a certainty. Its nutrition is no longer assured after its transport into the tissue of the host.

In spite of its death, the transplanted fragment contracts an intimate adherence to the bed in which it is placed. This adherence is at first fibrinous, then fibrous. In this case, it is currently said that the graft has taken.

Soon the connective tissues of the host penetrate into the cavities of the transplant, rehabilitate it progressively, and erode its bone substance, which, little by little, is rarefied

at the same rate that it is rehabilitated by the connective tissue. From this there results automatically the freeing of calcareous materials which soon bring about in the surrounding connective and interstitial spaces the formation of new bone. All this transpires according to the general laws of ossification. Thus, little by little, through the complete replacement of the transplant, the end sought for is attained, that is to say, the formation of solid bone. However, union may be lacking and the transplant may remain inert and be tolerated like a prosthesis. In other instances it can be eliminated like a sequestrum or completely absorbed without having bone built up at its expense.

II. DEATH OF THE TRANSPLANT

Bone tissue, having a low vitality, does not survive complete interruption of its circulation. Its nutrition is precarious and difficult. The mere fact of its having been freed from the surrounding tissues in all likelihood suffices in many cases to cause its death. Moreover, until definite union occurs the transplant can maintain its nutrition only by diffusion. The latter is very slow and very difficult. It would be astonishing if a bone graft could survive. *A priori,* reflection on the conditions of its removal from its normal position and on the mechanism of the life of bone tissue indicates that the death of the transplant would seem inevitable. Facts demonstrate that this is the case. This is a fundamental conception which at the present time is definitely known to be true.*

The first visible sign of death in bone cells consists of

*The low vitality of bone tissue renders it more liable to survive complete interruption of its circulation than would a tissue of higher vitality. Instead of the question of the death of the transplant being considered solved as the authors state, it is highly probable that transplanted bone has a better chance of living than do transplants of almost any other tissue. The truth of the matter probably lies between the two extremes; in other words, it is probable that in transplants of small bone fragments attached to the periosteum all of the transplant lives, while in transplants of large pieces of bone it is probable that cells in the interior of the transplant eventually die, while those near the surface continue to live and function. It is for this reason that transplants of living autogenous bone are more often successful than are transplants of dead bone.—*J. A. K.*

the transformation of the cytoplasm which undergoes autolysis. This is of a rather slow evolution. The bone cells, being elements with an extremely sluggish life, contain few proteolytic ferments. Autolysis is signalized by the appearance of clear vacuoles and fatty globules (autolytic fat) in the cells. The protoplasm appears flattened to the wall of the bone cavity, which is otherwise filled with a large clear vacuole.

As always in such phenomena, the nucleus preserves its staining properties for quite a long time. It is very resistant to autolysis. Also, it would be erroneous to conclude that a given cell is alive because of the presence of a nucleus which retains its staining properties. This error of interpretation has been the source of many errors in pathology.

Later, the cellular nuclei little by little lose their staining properties. The dead body of the bone cell progressively dissolves and vanishes from our eyes. The bone cavity then appears empty.

The cellular elements contained in the Haversian canals of the transplanted bone also die and disappear by autolysis, slowly, however. The red blood cells, walled off in the capillaries, hemolyse only later. They remain approximately normal in appearance during a rather long period. Thus is explained the fact that certain surgeons have thought that they saw oozing of blood from a graft several days after it had been placed in its new bed. In reality, the bone empties itself of its unchanged red blood cells.

In truth, it is often difficult to determine whether or not a bone fragment is dead. Only methodical microscopic study can tell this. There is no criterion as to the life of a transplant except the histological appearance of the cells.

Does the transplant die entirely? At its surface, conditions of nutrition are obviously better and oxygen can

reach the cells by diffusion. It is possible that bone cells remain living and more especially those which are found under the periosteum.

But if this eventuality is theoretically possible, it does not change the biological phenomenon at all in a general sense.

The question of the death of the transplant should be considered solved. It is thirty-two years since Barth conclusively showed it. It is truly a waste of time still to seek to verify facts so well demonstrated.

III. UNION AND REHABILITATION OF THE TRANSPLANT

The transplant, dead or dying, unites with the tissues of the host.

Union is at first purely fibrinous. The extravasated blood and lymph coagulates in more or less thick layers, according to location. This welding is at first realized by thin filaments of fibrin. Afterwards this organizes. Little by little it is invaded by connective tissue cells which push out into the clot. These elements, arising from the bed of the transplant, therefore appertain to the connective tissue of the host. This occurs from about the fourth to the eighth day. When coaptation is excellent and the fibrinous uniting mass is thin, fibrous union is rapid.

Movement is unfavorable to it, infection more so.

What we know of the connective tissue organization of the clot allows us to believe that the fibrinous organization in the beginning will have a great influence on the ultimate outcome of the transplant. The arrangement of the first fibrinous network determines the direction of the penetration of the cells and the disposition of the first collagen fibrils. Consequently, it is in this way that the fate of the transplant is at stake in its first few days.

The quality of the receiving connective tissue plays an equally important part. It is necessary that it be young. When it is sclerotic, organization of the clot does not take place well and the graft does not take.

The connective tissue of spongy bone is particularly favorable and revivifies with great rapidity bone which is enclosed by it. It is perhaps for this reason that implantation of a transplant in the medullary canal from both directions is not a good fixation procedure. The portion pushed into the bone is rehabilitated and resorbed before the intercalary portion of the transplant can be revivified and thus bring about the union of the fragments.

But it is in the results of transplantation made in the neck of the femur, for subcapital fractures, that one finds the most evident demonstrations of these facts. The clinical observations of Delbet supply experimental papers of great value on this point, since one sees here that all sides of the transplant are imbedded in spongy bone and are very rapidly absorbed, even if it is a transplant of dead bone; while the extra-osseous segments of the transplant are scarcely affected.

After the purely fibrinous union there follows fibrous union, in the same manner as in the organization of callus; there is a fibrinous and a fibrous phase.

The connective tissue fastens itself to the roughened surface of the transplant. It first grips and then penetrates it.

The connective tissue invasion is very extensive. It invades the Haversian canals, the contents of which are dead, and rehabilitates them.

Along with the connective tissue new blood vessels are formed. And at this stage the transplant is in reality made up of interstitial bone substance, a part of the transplant, and a vascular connective tissue which is derived from the host.

The rehabilitation of the transplant has been noted and pictured for a long time. Its importance does not seem to have been appreciated at its true value. It has been considered as a curious accessory phenomenon and without practical significance, whereas from the biological and practical point of view it is of the utmost importance.

It is true that it has been more often unrecognized in the transplants of living bone, and observed in the transplants of dead bone. This is because in the case of the latter the presence of Haversian canals furnished with young and living connective tissue in the midst of a dead bone permits one not to doubt that the transplant has been rehabilitated. It is for this reason that in 1882 Lannelongue and Vignal, in studying the outcome of splinters of dead bone sunk in a healthy bone, noted that they had been invaded by new embryonic elements with vascular granulating tissue insinuating itself into the Haversian canals.

The rehabilitation is made only in the Haversian canals. Only these cavities have a caliber large enough to permit the entrance of new vascularized connective tissue. The cavities of the bone cells remain empty. They are never again filled with living cells because no new cell is capable of penetrating into them. Even microbes cannot.

The rehabilitated transplant presents an interstitial substance with empty bone lacunae and Haversian canals filled with connective tissue having a living aspect, with capillaries filled with blood. If it is incised it bleeds more than a normal bone, because the capillaries are larger and more abundant than in a bone in process of rarefaction.

Radiographically, the transplant gives an image identical with that found immediately after the operation. X-ray examination does not distinguish whether it is dead or revivified. The thing that governs the type of radiographic image is the relationship between the quantity of calcified bone and the quantities of connective tissue which is not calcified; in short, the amount of calcium. But the plate

does not show whether either is alive or dead. The radiographic image is modified only by an advanced rarefaction. Great changes in the proportion of the calcified tissues are necessary for them to be visible.

Numerous factors influence the rehabilitation. In the first place, elementary mechanical factors.

It is first necessary to view what may be called the permeability of the Haversian canals. The auotlytic liquefaction of their contents is not always regular. Tissue débris can obliterate the canals and block the progress of rehabilitation by the connective tissue.

In the same way, bone powder formed during the operative procedure can obstruct the openings of the Haversian canals.

Reasons of this kind thus explain why transplants of spongy bone take better than do those of compact bone. The passageways for the rehabilitation are larger and more permeable in the first case than in the second.

In the same way, the favorable experimental results of a preliminary preparation of the transplant are explained. Brooks (1919) established in a systematic manner the transplantation in two stages. In the first stage, the transplant is cut on the donor, but not removed, and its bed is prepared. In a second stage, several days later, the transplant is removed and placed in its new bed.*

Under these conditions, the take is more rapid and the osteogenesis of better quality. The biological explanation of this fact is simple: the preliminary preparation leads to a rarefaction of the bone and consequently augments the permeability of the passageways for the rehabilitation. Muller (of Saint Etienne) proposed in the same spirit to criss-cross the graft, better to assure its take. These technical views are legitimate.

*Clinically I have used the two-stage bone graft three times for nonunion of fractures, and each time the transplant was successful. I modified Brook's method in that I merely cut the graft at the first operation and left it in its original bed. About two weeks later a second operation was performed and the bed was prepared and the graft placed in it. The preparation of the bed at the time of the transplantation enables one to get an accurately fitting graft and thus perform a better operation.—*J. A. K.*

As to ideas of the same order, let us note this apparently paradoxical observation of Chutro, that the bone graft unites better when the transplanted bone is affected by extensive trophic and nutritive disturbances. These disturbances result in a rarefaction which automatically increases the permeability.

Rehabilitation depends furthermore on the activity of growth of the connective tissue of the receptor. This is an example of the preparation of the ossifiable medium of which we have spoken at length. We will not revert to it. Perhaps it is in the same way that the well-known influence of the general condition and of certain endocrine glands have their influence.

Connective tissue extension depends in part on the growth of the blood capillaries, and this is reciprocal. It is thus, for example, that a fibrous connective tissue envelope will generate the vascular outgrowths into the Haversian canals. Rehabilitation may be hindered by it.

Finally, the regrowth in the Haversian canals is influenced even by the properties of the bone substance which forms the walls of the canals. This appears clear when one studies the slow rehabilitation of bone killed by chemical substances which are absorbed by bone. Under these circumstances it is modified and the connective tissue outgrowth takes place poorly as if the bone were toxic to it.

It is probably through an action of this sort that the variations of behavior of auto-, homo-, or hetero-grafts are to be explained. The tissues of the transplant harmonize more or less well with the connective tissues of the host which are rehabilitating the transplant. It is even possible to have absolute incompatibility from this source. This is the explanation of the superiority of the auto-plastic transplant, which is much more surely rehabilitated.

It is possible, besides, that by preliminary preparation of the transplant, soon this incompatibility will be made

to disappear. In this direction, the researches of Lickteig are most interesting; with the aid of human serum he prepared transplants of swine bone and in such cases saw these heteroplastic grafts give remarkable results.

IV. RAREFACTION AND ABSORPTION OF THE TRANSPLANT

The rehabilitation of the transplant is constantly followed by resorption of the fundamental bone matrix. This phenomenon is only a particular case of the process of rarefaction. It is conditioned by a vascular phenomenon.

The resorption of the bone matrix takes place at the periphery and in the interior, along the walls of the Haversian canals, into which new tissue has grown. The wall is attacked, and little by little it is dissolved. The canal enlarges and the transplant rarefies. It is the same phenomenon as that which occurs in the ends of the fragments of bone in fractures. But in the case of a transplant the connective tissue of the host resorbs bone substance which is foreign to it.

The resorption of the graft is further accelerated and made clearer according as the rehabilitation has been more rapid and more accentuated. The speed of resorption is dependent on the surface subjected to attack by the connective tissue.

Hard, compact bone, that is to say, one with narrow Haversian canals, is less favorable to rehabilitation and infrequently rarefies. It can unite by its surface without being repopulated by living cells from the host. This explains the extremely long tolerance of certain transplantations, such as in the extensive epiphyso-diaphyseal grafts, whether homo- or heteroplastic, as in the case of Küttner, who transplanted 18 cm. of the femur of a cadaver with success, and who made the transplantation of a fibula of a monkey to replace one congenitally absent.

For several months or even several years, nothing appears to change in the transplant. Radiographically there is no decrease in the density of the bone shadow. One might believe that there was a true bone graft. But if one waits, there always comes a time when the radiographic shadow changes. Shortly afterwards there is either an epiphyseal separation or a spontaneous fracture. The rarefaction has slowly done its work. But the hour of ossification is past. Peripheral reconstruction is no longer possible. One will find examples of such cases in the works of Simon.

It is easy to note the resorption of the transplant, macroscopically and microscopically. Thurlow and Macklin (1918) have proved this by using as a transplant a bone reddened by madder. The red graft, united with a white bone, gradually disappeared and was progressively replaced by uncolored bone. The disappearance of the transplanted bone is thus clearly indicated.

The rarefaction of the transplant changes it. It becomes less hard. One may cut it with a knife or scissors.

It bleeds more readily, as do the fragments of a fracture in process of rarefaction. It becomes more fragile and crushes and breaks easily. This explains the displacements and spontaneous fractures.

The repair of the fracture of a transplant takes place readily if there is no displacement. The rarefied bone tissue is in good condition to furnish a typical callus, in the ideal ossifiable medium which the hemorrhagic focus presents in consequence of the fracture. Many authors have studied this phenomenon. (Phemister, Robert Jones, etc.)

Histologically, one may detect the first signs of the rarefaction towards the tenth or fifteenth day. With radiography, in the present state of its technic, it is several weeks and sometimes months, especially for grafts of compact bone, before modifications of the usual shadow are perceptible.

Rarefaction of transplants takes place especially through osteolysis, and to a very slight degree through osteoclasis. It is subject to the conditions which we have studied above. It is useless to repeat them. Whatever its exact mechanism may be, the resorption of the transplant has a very important result from a practical point of view. It conditions the formation of new bone in the young connective tissue which has overspread the graft. One cannot repeat too often that, in order that a transplant may give definite results from a surgical point of view, it is necessary for it to be resorbed.

Commonly enough, surgeons still think that a graft which is resorbed is a badly nourished graft, and, on the contrary, that a well-nourished graft resists resorption and is well grafted.

It is exactly the contrary which takes place. When a graft is well nourished, that is to say, richly vascularized, by blood vessels which have grown into its Haversian canals, the rarefaction is maximal. When it is not revascularized, when it is poorly nourished, it is not rarefied and it is not grafted; it is only tolerated. In the latter instance the transplant is not a graft, it is only a prosthesis. This may be excellent from a practical point of view. But the goal sought in such cases has not been attained.

It is still too commonly thought that there is only one way for bone to disappear: elimination after the manner of a sequestrum, whereas the total or partial disappearance by progressive rarefaction is a common phenomenon.

Let us repeat once more that rarefaction is the condition for the success of the graft. Far from combating it, the surgeon should seek for it.

V. NEW BONE FORMATION

The rarefaction of a transplant is normally followed by its ossification. The two phenomena are bound together. The first conditions the second, which follows it closely.

The new formation takes place in two areas.

It takes place first of all in the connective tissue which surrounds the transplant at the two extremities, and then gradually along all its length. The whole delineates a kind of hourglass.

Here again, this new ossification is not the result of a growth of the transplant, nor of a culture or proliferation of the bone tissue which constitutes it, since the latter is dead. The host has furnished the connective tissue matrix. The transplant has provided the calcium material. In this process the renewal of the calcium salts is essential. In

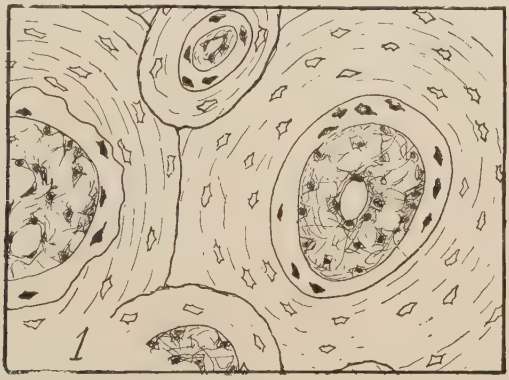

Fig. 30.—Regrowth of dead bone. New bone formation in the interior of the Haversian canals of the transplant.

grafting a decalcified bone, Barth obtained only a fibrous scar and never new bone.

Here again one finds the parallelism so exactly fixed between the degree of bone rarefaction and that of the formation of new bone, already noted in connection with the repair of fractures. Phemister, in a very conclusive work, has given pictures which clearly show this parallelism, all the more conclusive because he has not sought for their explanation.

New bone formation is also produced in the interior of the transplant. In the Haversian canals enlarged by the

rarefaction, new bone lamellae are deposited, as a result of the metaplasia of the layer of connective tissue next to the bone which fills these canals. What takes place around the transplant also takes place in its interior. The phenomenon is the same. It is a metaplasia of the connective tissue of the host.

Histological study shows it very plainly. The fundamental bone substance is dead, with empty cellular cavities. The Haversian canals are enlarged. On the dead bone substance one sees a layer of bone different from the substance of the transplant in its staining properties and in the presence of bone cells of a young type, very much alive, with an abundant protoplasm and a voluminous nucleus. The contrast between the two varieties of bone is striking.

This new bone formation signifies that the transplant is integrated gradually to the skeleton of the host, not as a result of a true graft with survival, but by a real substitution. The transplant has served as a guide and as a furnisher of calcium. It is only the case of a new ossification by tissues from the host on soil furnished by the graft.

The factors which govern this new formation are the laws of ossification of which this is only a particular case. The influences of the general condition of the subject (humoral and vascular) and the influence of the local factors are here mutually combined.

The first rudiments of new bone appear at the earliest towards the fifteenth day, in man, and more rapidly in the rabbit than in the dog. The formation of bone in the Haversian canals is much more slow, appearing only at the end of several months. It may be absent and the resorption is continued until there is complete disappearance of the transplant.

We are in complete ignorance of the late phenomena of the "taking" of grafts.

VI. SELF-PRESERVATION AND ADAPTATION OF NEWLY FORMED BONE

In the beginning reconstructed bone has the form of the transplant. If one waits several months or several years it is completely identical with the general line of the bone on which it is grafted. At the end of several years it is impossible, in the most favorable cases, to recognize radiographically and clinically, that complicated biological operations have taken place here.

What are the phenomena which lead to this result? One can only conjecture them, for documentary evidence on this subject is totally lacking.

We think that it is function which directs the preservation, growth, and adaptation of the newborn bone in the transplant.

We apply to this particular case the views which come from the study of bone morphogenesis. But, in reality, definite information is lacking. Except for radiography, one cannot follow the slow evolution of a transplant.

We know the initial mechanism of the formation of bone, but not that of its internal growth. It should be noted that the quantity of bone finally produced is much more considerable than the quantity of bone grafted, notable in osteoperiosteal grafts.

Whence come the elements of this growth which continues? One can make probable suppositions, but there are no facts which permit one to state it accurately. It is the particular aspect of bone grafting which would be most profitably studied at present.

Side by side with the growth and parallel with it, is the preservation of the transplanted bone. There is reason to speak of it, since certain transplants disappear without leaving traces.

Function here plays an important part. But this expression conceals a complete ignorance of the mechanisms at work.

Nothing is more justifiable, theoretically, from a physiological point of view, than the early exercise of the extremities in which a bone graft has been placed, exactly as in the case of fractures.

But again it is necessary to come to an understanding as to the value of the word *early*. By mobilizing too soon, one runs the risk of fracturing the transplant. With long immobilizations, surgeons have obtained remarkable results. Consequently mobilization should not begin too early, because of the risk of passing beyond its useful limits and bringing about injuries to the model in process of construction. About three months is the minimum time for immobilization for a transplant of from 10 to 15 cm. in length.

The study of these phenomena of late adaptation can determine not only therapeutics, but all bone biology in a direction which we cannot even foresee at the present time. From the practical point of view alone, one can believe that it would be fertile.

Up to the present, surgeons have had no other ambition than to succeed technically in the operative intervention (the word technic being taken in its larger sense). But actually where under given conditions one is approximately certain of the results, one can have larger ambitions and dream of a distant future.

VII. TRANSPLANTATION OF DEAD BONE

Living bone dies in its entirety when it is transplanted. Is this equivalent to saying that one can consider a transplantation of dead bone as the same as a transplantation of fresh bone?

The question has been much studied experimentally. These studies have shown that dead bone comports itself in the same manner as does living bone as far as the general phases of its evolution are concerned. It unites, is

rehabilitated, is resorbed, and is invaded by new bone exactly the same as bone taken from the living. But it is indubitable that the phases of this evolution take place more slowly and less regularly than they do with living bone. Transplantation of dead bone approaches heterotransplantation. The explanation of this undoubted fact is not yet known. One may admit provisionally that an explanation similar to that which is given for the transplantation of thyroid glands, for example, may exist. The dead tissue, like heteroplastic bone, greatly accelerates the formation of a sclerotic tissue around the transplant. This sclerosis hinders the penetration of new vessels into the Haversian canals and consequently hinders the formation of new bone. This is not produced, or is produced only slowly, about a fragment of tissue from the same individual, when compared with its production around a graft taken from an individual of the same family. Recent works of Leo Loeb on grafts in general are very suggestive in this connection.

It is equally possible that dead bone has canals which are only slightly permeable. The manner of killing the bone comes actively into play in this respect. In repeating the very old experiments of reimplantations of trephine buttons, but after having killed them, Cornil and Coudray were never able to obtain a take. But when one studies their experiments more closely, it is seen that they killed the buttons with solutions of sublimate. This toxic agent sufficed to render the bone uninhabitable by the connective tissue which attempted to invade it.

Bones killed by prolonged boiling are rehabilitated with difficulty. Boiling alters the collagen, the fundamental matrix of osseous tissue. It swells it. This is perhaps one of the reasons for the bad results obtained in experimental conditions.

In short, as with the transplantations of nerves, tendons, etc., the way in which the bone tissue has been killed and

in which it is preserved is of capital importance. It would be very desirable if systematic researches would be made in this direction. They would lead probably to fertile theoretical and practical results.

In any event, at the end of a certain time, the condition of the graft is identical whether it is a question of dead bone, living bone or the bone of another animal. An experiment of Hey Groves is very instructive in this regard. In a cat's tibia, he made in the fresh state three troughs. In each he placed a similar graft: in one, the bone was taken from the same animal; in the second the bone was taken from another cat; and boiled bone was used for the third. After six weeks, microscopic examination showed no difference between them. None of them contained living elements. All of them were dead; but all were in process of resorption without there being any difference between them.

Thus, from the biological point of view, transplantations of dead bone comport themselves exactly as do those of living bone. And from this it is to be concluded that the question should not be practically abandoned. Entered upon in turn with enthusiasm and abandoned as being valueless, the transplantation of dead bone is not yet settled, practically speaking. The few remarkble successes obtained have more theoretical value than the numerous failures which have been recorded. When one has seen a transplant of a dead bone fracture and repair its fracture, this is an indication that its biological life is unfolded, under certain conditions, exactly as is that of an autoplastic transplant. It is not legitimate to believe that the matter has been settled beyond appeal. What is lacking perhaps is the proper preparation of the dead bone which we do not know how to prepare. The researches of Lickteig are very suggestive in this regard. Investigation should be directed towards the study of this interesting problem on which therapeutics waits for so much.

VIII. ROLE OF THE PERIOSTEUM IN THE EVOLUTION OF A TRANSPLANT

By reason of the physiological importance classically attributed to the periosteum, it has been attempted for a long time to determine its part in the uniting of transplants. Is the evolution of a transplant better according to whether it does or does not possess its periosteal covering?

In the view of Ollier, the part of the periosteum in grafts was fundamental. In contrast to bone it always survived. To him it was the agency of the graft. It was he who realized its adherence to, and later restoration of, the bone. He believed that a bone freed of its periosteum could not be grafted, and that it always died.

It has been seen, in regard to the rôle of the periosteum, that this positive opinion can no longer be maintained. But all experimenters have reached this conclusion, that though the periosteum is not indispensable to the uniting, rehabilitation, resorption, and ossification of the transplant, it indubitably favors these phenomena. The presence of a fibrous layer on one surface of the transplant has a series of advantages. It constitutes, in the first place, a medium for the ready diffusion of the elements of nutrition, mobilized in a soluble form. Consequently, it favors the fibro-osseous union of the transplant to its bed.

The existence, thanks to the periosteum, of better nutritive conditions explains the possible preservation alive of the most superficial layers of the periosteum, and, thanks to it, of the bone cells found there. We have admitted this survival as possible. In truth it is of an importance which is rather more theoretical than practical. It is realized in an extremely slight thickness usually of the order of a tenth of a millimeter. But slight as it is, it can be of

advantage. From this point of view, the results of experimentation can be superimposed on those of clinical observation; results are better with the transplants having periosteum than with those that lack it. In this we are of the same opinion as Axhausen.

The second advantage of the conservation of the periosteum is in bringing with the transplant a connective tissue layer which is particularly fit for bone metaplasia. This is one of the properties of the periosteum surrounding the transplant. New bone formation will be made quickly and well. Histological examination, like radiographic exmination, clearly shows this.

But it also happens at times that the periosteum by its presence is harmful to the take of the transplant. This is what transpires with very fibrous periosteum.

Fibrous tissue interferes with the growth of capillaries and of connective tissue into the Haversian canals. When the latter are covered with periosteum, rehabilitation is retarded or does not occur. The union of the transplant takes place quickly and well, but not its indispensable repair. The latter is very tardy. These ideas seem to permit explanation of the sudden and late resorptions (after several months) which are sometimes observed in man. All this takes place as if there were acting a periosteal barrier which could be passed but slowly by the vessels.

Another advantage of the periosteum is that it shall didirect the bone growth (Baschkirzew and Petrow). The periosteum is a limiting membrane which prevents the bone from going astray and in some way losing itself. On the other hand, it also hinders and limits the outgrowth of vessels, and hence limits resorption. It is an agency of bone condensation. It is in this way that one should interpret the saying of Murphy that the periosteum is bone-conductive.

IX. GENERAL CONSIDERATIONS AND CONCLUSIONS

Now that we know well the succession of the biological phenomena which are at the bottom of the reconstruction of a graft by the tissues of the host at the cost of its destruction, one may ask oneself whether the result obtained truly represents the therapeutic ideal.

The rehabilitation, rarefaction, and reconstruction of a transplant are delicate operations that we do not know how to control and which always allow some incertitude to arise as to the therapeutic result in view of the reason for undertaking the transplantation.

We know, however, that dead and fixed tissues are composed of inorganic materials which are capable of uniting to, and remaining included in, the living tissues like ideal prosthetic parts for a number of years. In like technical conditions, one can ask at this point whether or not it is preferable to deliberately include organic prosthesis in tissues rather than to subject them to the uncertainty of the biological taking of a transplant. It is evident that the employment of unabsorbable prostheses requires preliminary studies, fixing on the tissue reactions which they can provoke; but it is perhaps the ideal to pursue in future and we will not be surprised if this should be the eventual method in the reparative surgery of bone and of certain articulations.*

*Robineau (Journal de Chir., 1926, vol. 27, 151) reported the substitution of the lower 10 centimeters of the humerus by a prosthesis made of steel and covered with hard rubber. Six months after the operation the prosthesis was well tolerated and the patient was satisfied. He stated that there was some function in the elbow, but did not give the range of motion. The eventual result remains to be seen.—*J. A. K.*

CHAPTER IX

HETEROTOPIC OSSIFICATIONS

In the organism there are not several modes of bone formation. There is only one, and this is always the same. Also true spontaneous experiments, such as are found in heterotopic ossifications, reveal with the greatest clearness the fundamental factors which come into play in osteogenesis. It is for this reason that we believe it useful to give several pages to their pathogenic mechanism.

The fact of the existence of heterotopic bone being beyond question, four opinions have been advanced to explain their origin.

Cohnheim said that all heterotopic ossification was the result of the growth of a latent nodule of embryonic bone. This conception is beyond discussion. It is impossible to prove that an abnormally placed ossification does not originate from an embryonic inclusion. But no one has ever been able to demonstrate one of these latent bone germs. This theory, three-quarters of a century old, has lasted long enough and should not be revived.

In the view of Ollier all heterotopic ossification follows periosteal displacement. One understands that, in accordance with the classical ideas of bone formation, this explanation has had some probability when it was a question of interpreting a juxtaosseous ossification in muscle tissue (so-called local posttraumatic myositis ossificans).

But of what value is it when one tries to understand the formation of bone in a laparotomy scar? Lacking general value, the theory of Ollier is without application. It should be abandoned.

Busch, Macewen, and Ribbert have thought that the matter could be explained by the sowing of osteoblasts. And extending this theory in an effort to make it harmonize

with the known facts regarding heterotopic bone formation, Macewen admitted that the osteoblast can migrate in the blood like a common leucocyte and that thus is explained all abnormally placed bone. All this osteoblastic metaphysics has not the least histological argument to support it. It is waste of time to essay the demonstration of its impossibilities.

Myositis ossificans is still spoken of. But this inflammatory hypothesis, to which certain objections may be raised even when the question is merely one of intramuscular ossification, has many irrefutable objections and really cannot be advanced at all when one attempts to explain the origin of bone which is included in the wall of an aneurysm or in a mass of organized blood clot.

It is hence necessary to seek elsewhere than in the proposed explanations the mechanism of the formation of heterotopic bone.

Whatever may be the heterotopic bone which one examines, whether its site be in a muscle, in a scar, in clots, or even in a gland, it is never formed except in connective tissue in which are found bone trabeculae. Osteomas of the intestine exist, but bone in this location is formed only in the connective tissue. There is in the bone itself no intestinal epithelial débris. It is necessary always in returning to this point to remember that bone is always a connective tissue formation.

Granted that bone may be seen everywhere that connective tissue is found, but not elsewhere, the explanation should be valuable for all localizations of heterotopic bone. It is in its generality that one should recognize its explanatory value. It is self-evident that the general rules of all osteogenesis should apply here integrally.

We will review successively: the general mechanism of heterotopic ossifications, the mechanisms which enter into some of them, and the research made on the experimental production of heterotopic bone.

I. GENERAL MECHANISM OF FORMATION

When one examines specimens of heterotopic bone—and we have seen them almost everywhere: old hematomata, wounded nerves, walls of aneurysms, muscles, laparotomy scars, etc.—one discovers in them the succession of the two fundamental processes of all ossification, namely, the creation of an ossifiable connective tissue medium and the setting free of calcium material in the immediate vicinity.

The first of these processes resides in the formation of a proliferating tissue. This always takes place by the organization of a blood clot or by the reversion of the connective tissue to an embryonic state on account of traumatic or infectious inflammation. There is not a single heterotopic ossification in which one of these two mechanisms cannot be found.

The second process consists of the liberation of calcium material in the immediate vicinity of the ossifiable connective tissue material. This is brought about by the resorption of a calcified deposit. This is the case in all heterotopic ossifications. They are always developed in the vicinity of an accumulation of lime salts. The nature and origin of this calcified deposit can be very variable, but it always plays exactly the same rôle as does bone in process of resorption in surgical osteogenesis after periosteal stripping of bone at the ends of the fragments in the process of resorption in the repair of fractures, and it plays the same rôle as does the transplant in bone grafting. The resorption, causing the freeing of calcium material, lends to this local calcific excess which is essential for the production of ossification.

In the course of the formation of heterotopic ossifications the following different phases should be reviewed. They are evidently more or less confused, but always distinguishable:

1. Formation of the ossifiable medium.
2. Calcium deposition and its resorption.
3. Formation of heterotopic ossification.
4. Fate and preservation of this ossification.

A. Formation of the Ossifiable Medium

Here as elsewhere the matrix of new bone is formed of young connective tissue. This arises from a reversion of pre-existing connective tissue to the embryonic state. The reversion may be due to either of two conditions: organization of a blood clot or infectious or traumatic inflammation of normal connective tissue.

As a rule, the proliferating tissue arises from the organization of an extravasation of blood. At the bottom of many heterotopic ossifications there is a history of hematoma.

This tissue is organized in a manner that is well known, and here again we fall into perfectly definite conditions. A circulatory régime maintains an edema which is identical with that which we have described under the name of preosseous edema. This tissue is at a definite moment ready for ossification. Then the initial clot has become an ossifiable medium.

In other circumstances, it is because of a traumatism without hematoma or of an infection of slight virulence that connective tissue or a fibrous scar reverts to the embryonic state. There is nothing surprising in this reversed evolution of adult tissue. It is a commonplace phenomenon which, in this particular case, derives its peculiarity from the mere circumstance of taking place in the vicinity of a calcified focus. One might say without paradox that at any given moment there is taking place at some point in the organism a connective tissue evolution which results in the formation of areas of the type which constitutes the ossifiable medium; but that no heterotopic bone is formed,

for the simple reason that there was no calcified focus in the vicinity.

B. The Calcified Deposit. Its Resorption

All heterotopic ossification takes place in the vicinity of a calcified deposit or of a point of phosphocalcific concentration.

A priori, this statement seems surprising, and we are persuaded that it will be considered excessive and unjustifiable.

Let us examine the data.

The simplest example is ossification of a muscle in the vicinity of a bone. Here the calcified deposit is bone. Granting what we have said about the formation of callus, concerning the rôle of traumatic hyperemia in the setting up of a superficial bone resorption and the formation of parosteal muscle callus, one will be convinced that there is no great difference between the muscle callus of a fracture and a traumatic muscle osteoma.

Let us take more complex cases. Let us envisage ossifications far from any bone susceptible of entering into resorption.

In order to understand what will happen, it is necessary to recall a sort of a law of biochemistry. Every part of an organism which is dead or dying tends to become infiltrated with calcium salts. A kind of progressive petrifaction takes place, and there are numerous examples of this. Let us cite calcified tubercles, calcified fibromata, lithopedions, calcified goiters, pleural calcifications in old pleurisies, etc. These examples can be multiplied. Experimentally, one can obtain this calcification and certain experiments permit one to follow the deposit of calcium in dead tissue. From this standpoint the experiments of H. G. Wells deserve to be recalled. Fragments of killed cartilage were placed in the tissues or in the peritoneal cavity, the calcium content having been previously determined. At intervals more or

less long, these cartilaginous fragments were removed and the calcium which they contained was determined. In this manner one can see a calcification progressively established.

Observation shows that all heterotopic ossification takes place in the vicinity of a focus of this kind. The substance capable of fixing calcium can be of a very variable nature: cartilage, tuberculous caseation, fibrinous deposit, elastic fibers in regression, muscle fibers, remains of fascia or altered aponeurosis, etc. The routes of approach of the calcium salts can likewise differ according to the case: transport by normal capillary circulation, diffusion by the interstitial lymph or fluids of the serous cavities, or they may be taken directly from the circulating blood in the case of calcification of the great vessels, etc.

The intimate details of the process are unknown. What conditions come into play in this phenomenon of the diffusion of complex calcareous substances and in their fixation by the proteins? Why should a grafted living tissue degeneration in situ appear to fix more calcium than when it is transplanted after having been cut as a preliminary step (experiments of Andre)? The answers to the above questions are still unknown to us.

One can inquire as to the significance of the calcareous deposit and why young connective tissue does not directly fix the calcareous materials circulating in the blood. Why this intermediary? Stated in this form the question is obscure. The calcareous deposit is not made for the purpose of giving rise to a heterotopic ossification. It is formed without predestination. And it is very fortunate that young tissue is incapable of fixing calcareous material circulating in the blood. Were this not so we would be petrified rapidly.

This intermediary stage is therefore indispensable. Lecène has attempted, without results, to inject various lime salts about the sites of inflamed connective tissue. Even

the deposition of ossifiable substances such as the ash of sea shells, egg shells, etc., about an ossifiable medium does not lead to ossification. It is necessary that the calcium should be first fixed on an organic support and taken up again by the organism in a certain form which is still unknown. In anthropomorphic speech, one might say that it is necessary for the organism itself to prepare the calcium which it needs for the formation of the bone which it builds up.

In reality, the calcareous deposit is not present for ossification. The latter is a fortuitous phenomenon, resulting from the chance juxtaposition of a connective tissue in an embryonic state and a collection of calcium in a definite form which is as yet unknown to us.

This calcium mass appears to us immobile. Perhaps it is not so. We have proof only that it is partly mobile, because of the observation of neighboring ossification which is the evidence of it.

How is the calcium displaced? We do not at all know. It is certain that it is accomplished in a humoral way, but we do not know the details of the process.

Histologically, resorption of masses of calcareous material takes place in two ways, either by a humoral type of dissolution, apparently without the cells coming into play (osteolysis), or through a phagocytic attack with the intervention of giant cells analogous to osteoclasts.

At certain points, for example, in calcified cartilage, one notes figures quite comparable to those which reveal themselves in epiphyseal cartilage (formation of cavities by invasion of proliferating tissue).

C. Formation of Heterotopic Ossification

When an embryonic connective tissue which has become ossifiable and a collection of calcium are brought together

by chance, ossification takes place by the usual processes. The disposition of the heterotopic ossification is determined by the architecture of the medium in which it develops. If it is such tissue that models the bone formation and makes of it a plaque, a nodule, splinter, etc. Often when it attains a certain volume there forms a central cavity which is sometimes spoken of as a true medullary canal.

Smaller formations reduce themselves to a few bone trabeculae.

D. The Fate and Preservation of Heterotopic Ossification

The phenomena of secondary changes can be produced. Heterotopic bone has exactly the same biology as normal bone. The same morphogenetic influences act on the development of its architecture.

It is necessary to note here that the natural tendency to resorption is counterbalanced by the existence of sluggish blood circulation.

The frequent presence of fibrous elements about the ossification, true periosteal limiting membranes, also tends to hinder resorption, and in this way to contribute to the maintenance of the ossification.

From this point of view muscle osteomas present peculiar characteristics. Their extension is much less limited and they may acquire a considerable volume, while all others are of very small dimensions.

Heterotopic ossifications beyond a certain volume have connective tissue spaces. Usually the latter are filled with nonadapted connective tissue, at times also by adipose tissue (fatty marrow). Bunting has reported the curious case of an heterotopic ossification the spaces of which were filled by hematopoietic elements (red marrow). This fact brings up the strange problem of the origin of these hematopoietic elements.

II. ON SOME PARTICULAR HETEROTOPIC OSSIFICATIONS

We will content ourselves with studying the mechanism of the formation of some heterotopic ossifications, especially those that we have met with. In all of them a calcium deposit is found.

A. Muscle Osteomas

These have been the most studied of all the heterotopic bone formations.

Histologically, they form masses of coarse bone tissue comparable to that of early callus. Their peripheral layers are denser than the central regions, especially in old osteomas which have had time to be developed and moulded. The central portion is rarefied and sometimes includes connective tissue spaces.

When the osteomas are younger and hence but little changed, striated muscle fibers in process of atrophy are frequently met with in their centers, just as one finds them in muscle or parosteal callus.

In the bone masses, cartilaginous nodules are often met with which are identical with those encountered in bone callus. This is a question of chondroid rather than cartilaginous tissue, the cells of which, lacking capsules, are of the fibroblastic type. At their periphery these nodules are generally surrounded by a thin shell of bone. Between the chondroid and the bone tissue there is the appearance of a direct transition. There are very clear examples of the chondro-osseous tissue which we have already noted.

Often also, the center of these cartilaginous nodules is more or less degenerated and at times truly liquefied. One then has a pseudocyst, forming what is called a cystic osteoma. This degeneration almost constantly affects the cartilaginous nodules and can cause them to disappear entirely. Then one finds nothing more than the bone shell

of the nodules. It might be said that there is here a matter of bone cyst, which is inexact.

At another time we have studied a very curious specimen of this kind, removed by Tisserand. An old osteoma oc-

Fig. 31.—Spindle of a 15-day-old new bone developed in the muscles (muscular callus). Bone growth takes place parallel to the muscular fibers. The figure represents a transverse section of this spindle. Laterally, the phenomena of limitation coincide with osteoblastic figures of a pseudo-epithelial type.

cupied all the tibialis anticus muscle. Its liquefaction, with the death of the bone, had made of it an immense cystic pocket full of spicules of dead bone.

Periosteal tears have usually been advanced to explain the formation of muscle osteomas. At first glance certain facts seem to give support to this hypothesis. There are osteomas which seem to be directly implanted in bone and the radiographic images increase this impression by superimposing shadows.

This is only apparent. A great number of osteomas have no bone connection and are developed entirely in the muscle, at a distance from the intact periosteum.

This fact is to be taken into account, and if it is remembered that the periosteum has no osteogenic power, one is compelled to agree that the periosteal origin is only a superficial idea resting upon a poor physiological interpretation.

All the pathogenesis of muscle osteomas becomes clear if one seeks for their origin in the fundamental processes that we have seen to be constant in osteogenesis. Here there is an ideal ossifiable medium, since the contusion which one always finds in the history of osteomas has produced a clot and a paralytic vasocongestion. The organization of this clot is automatically set up. If the traumatism has brought about bone hyperemia, resorption comes into play, calcareous materials are freed and the circle is closed. We have observed in radiographs this bone rarefaction in the vicinity of an osteoma. If one seeks for it systematically, it will often be found.

A stronger reason exists when there is a periosteal tear. But osteomas at times exist far from skeletal parts. The problem then seems impossible of solution. But in reality, if one searches the center of the osteoma with care, in sections, and at various points, one finds a circumscribed focus of calcification, generally a chondral strand more or less degenerated and calcified, and sometimes muscle fibers and degenerated connective tissue bundles which have fixed calcium.

The natural tendency of muscle osteomas is to disappear.

Traction and twisting play a great part in keeping them up. They determine the architecture of the osteoma in the direction of the muscle fibers. The osteoma can thus become definitive.

In short, that which maintains the osteoma is the permanence of the causes which have provoked it. The presence of a bone mass in a muscle gives rise to a continuous state of hyperemia around itself and in the neighboring bone. Moreover, the bone mass disturbs the neighboring muscle fibers and may tear them. It thus causes new hemorrhagic foci, new zones of edema. Often unseasonable attempts at mobilization or of massage add new complementary traumatism and in this way increase the growth of the osteoma. This is so true that it suffices to immoblize a limb in plaster absolutely for two or three months, to bring about the complete disappearance of the osteoma. We have personally observed this on two occasions.

If only this is done one will see an arrest of osteomas occur much more frequently and much earlier, and they will more quickly reach that stage which is so inexactly termed the maturity of the osteoma, that is to say, cessation of the local conditions which are suitable for the extension of the ossification. For as in all heterotopic ossification, osteomas have a natural tendency to disappear if they are not sustained.

This tendency of osteomas to disappear if they are not stimulated explains the frequency of the very curious osteoblastic deposits which are at times noted within them. Around osteomas with arrested growth, or even in regression, sections show margins of osteoblasts, forming zones which are almost epithelioid, and these may be so well developed that at times it is a question whether or not one is dealing with a sarcoma.

B. Ossifications in Vessel Walls and in Hematomas

In the necrotic foci which form in the walls of atheromatous vessels, there is produced habitually a calcareous

infiltration. When one takes into consideration these facts: first, that the blood is the vehicle for calcium, and second, that the intima and an important part, if not all, of the middle coat of the vessels are nourished by diffusion from the circulating blood, one readily understands the frequency of arterial calcifications. These arterial calcifications in their turn explain the formation of those microscopic bone strands which are sometimes found in the vessel walls.

The relation of these bone plaques to calcifications has been suspected for a long time (Monckeberg, Bunting, Harvey, Buerger and Oppenheimer, etc.). Paul thought that the bone plaques formed in fractures of calcified masses.

The bone plaques, which are not rare in encysted aneurysmal hematomas and in the walls of aneurysms, are probably to be explained by the same mechanisms. We have personally encountered them on three occasions, the bone being in the center of a fibrinous mass, far from all bone and periosteal contact, the bone and periosteum evidently being intact. We have even seen it in arteries long since sectioned by a projectile, even in the middle of the fibrous zone which represented the vascular trunk, which had been destroyed and spontaneously obliterated. In this case one easily grasps the mechanism of the formation of a connective tissue medium at the expense of the fibrin and the possibility of calcification of the dead tissue débris. But when it is a matter of an aneurysmal hematoma, the explanation is more difficult. It is difficult to see how the connective tissue can invade this mass of fibrin and how the calcific deposit can form. To speak truth, we lack specimens establishing the exact mechanism of the connective tissue rehabilitation and of the calcification. These bony plaques are fortuitous discoveries in the course of difficult operations. In removing a mass of clots, the hand suddenly encounters a little spicule of bone. One does not

look about for its connections, and the ultimate histological examination cannot fix these points. Moreover, it should be recognized that up to the present time no one has ever taken the trouble to seek for a calcareous plaque either in the true arterial wall or in the center of the zone of organization of an aneurysmal pouch. It would therefore be welcome if, in a case of this kind duly diagnosed (which is possible with radiography), one should take care to remove in a single block the vessel wall, that of the aneurysm, and the mass of clots containing the bone plaque. Perhaps the biological reason for the existence of this bone might thus be readily found.

The only observation, purely macroscopic at that, which we can give on this subject is that in one of our cases there was a calcified plaque in the exact vicinity of the zone of rupture. This calcification was certainly of recent origin since it arose from a war wound in a young subject.

C. Ossification in the Interior of Nerves

This eventuality has not been very rare in wounds of the great nerves by war projectiles, without there having been the least skeletal connection with them. Personally we have met with it three times. It was manifest that the ossified plaque was like a cast of an old intranerve hematoma, the projectile having passed through the nerve.

Whence comes the calcium in these cases? In the absence of research, it is impossible for us to say. But it is evidently in conditions where there is calcareous infiltration of dead débris that it is observed. As in the case of bone formed in the walls of aneurysms, we can only point out the direction in which research should be undertaken to reach a solution of the problem.

D. Ossifications About Necrotic Foci

Calcareous material and the hyaline connective tissue which surround old tubercles readily calcify. This is one

of the modes of healing of tuberculosis. Around these calcified foci it is possible for true bone to form.

Even in the arachnoid, the corpora amylacea, necrotic nodules of a still unknown origin are frequently calcified and bring about the formation of arachnoid bony plaques that Cushing and Weed (1915) have studied.

The mechanism of formation of these heterotopic bones is very much clarified by the experiments of Sacerdotti and Fratin. On ligating or on temporarily compressing the renal pedicle in the rabbit the appearance of heterotopic bone is brought about in the connective tissue and in the vascular walls of the kidney. The first consequence of the ligature is the necrosis of an important number of urinary tubules. These calcify the more readily because the urine is rich in calcium salts. Around these degenerated and calcified urinary tubules the connective tissue undergoes bone metaplasia. Here one readily grasps the mechanism of the formation of heterotopic ossification.

In the same way are to be explained the results obtained by Neuhof in the course of experimental researches on the closing of visceral losses of substance by free transplantation of fascia. In certain places, but on the bladder particularly and constantly, the aponeurotic graft gives rise to a plaque of true bone. It is easy to reconstruct the progress of these phenomena. In contact with the calcareous urine, the fascia necroses and is calcified. Around the borders of the old transplant a proliferating tissue is formed. In proximity to a calcium collection, it ossifies. It is always the same fundamental process. And these experiments undertaken without preconceived ideas are a rigorous demonstration of the mechanisms which we have advanced.

E. Ossifications About Calcified Cartilages

Cartilage which dies in the tissue is readily impregnated with calcium salts. It frequently occurs that bone

metaplasia installs itself in the young connective tissue which surrounds the impregnated cartilage.

About cartilaginous grafts nodules of bone frequently develop. We have published examples of this. The cartilage in these cases is always more or less calcified. The same mechanism comes into play in grafts of killed cartilage in the rabbit ear, as Nageotte has shown.

This ready fixation of calcium on cartilage is met with in other curious circumstances and explains the presence of bone metaplasia encountered in the most singular locations. It was thus that Asami (1920) studying ossifiable nodules in the uterine horns noted around them calcified cartilage, as well as connective tissue masses and vessels in course of hyaline transformation. It is probable that the first metaplasia was cartilaginous and that the cartilage functioned as a means of calling forth the calcareous salts.

In the same way, in the lungs, bone nodules have been noted in the vicinity of the trachea and the bronchial cartilage (Devic and Paviot, Mangini, Mailer).

Cartilage can remain partly living and calcify. One notes in these cases a kind of direct transformation of the cartilage into an imperfect bone tissue. It is to this type of cartilaginous ossification and not to a juxtacartilaginous ossification that the cases of bronchial ossification noted by Kitamura are related.

One should compare the mode of repair of fractures of the costal cartilages which always consolidate by means of a bone callus. Here the cartilage necroses and the fragments fix lime salts and constitute the calcareous deposit which brings about bone metaplasia in the proliferating tissue which is found as in an ordinary fracture.

F. Ossifications in Integuments and in Scars

The formation of true bone in scars has often been found, and this has been very intriguing. There is here no pos-

siblity whatever of the providential intervention of periosteum.

These ossifications form around calcified remains of fibrous or muscular tissues which are more or less altered in the course of the repair of the abdominal wall and along the sutures. Lacène thought that the interpretation of these facts ought to be sought for in a modification of the calcium metabolism which caused a scar, such as remained fibrous in most individuals, to become osseous in the case of certain others. It seems to us that here again it is rather a local cause which should account for the origin of these ossifications, which in general are small and which do not return after ablation.

G. Heterotopic Ossifications in Tumors and Heterotopic Osteoma

Bone is frequently encountered in what are known as mixed tumors.

This is explained by complex embryonic inclusions. Without entering into the discussion, it seems to us that it would be more legitimate to consider that the bone and cartilage found in these tumors are only metaplasias which are always possible in a connective tissue in process of evolution. At once the origin of these tumors becomes simplified. If one takes into account the frequency of zones of necrosis in these new growths, one need not be astonished that there can be points of calcification in them, and the latter are probably the origin of the bone plates found in such tumors.

From time to time one finds pedunculated osteomas in organs where there is no bone, such as the intestine, the fallopian tube, the thyroid body. It is probable that here again the same explanation holds. It is at least in this direction that research is to be made.

III. RESEARCHES ON THE EXPERIMENTAL PRODUCTION OF BONE IN MAN

The study of heterotopic ossification in scars leads us to give the results of researches undertaken in 1917 on the experimental production of bone in man, in the absence of periosteum.

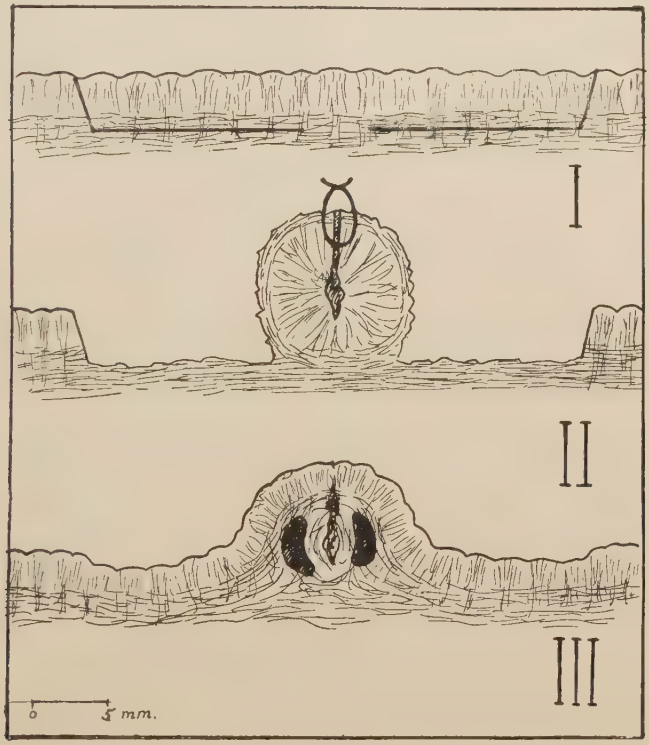

Fig. 32.—The experimental production of bone in man. Steps in the experiment. *I*, transverse section of the wound, arrangement of the incisions. *II*, formation of the tube. *III*, arrangement of bone spicules.

Our end was to bring about, in young connective tissue, the transformations, especially edematous ones, necessary to the setting up of bone metaplasia. We thought that we could accomplish these modifications by proceeding in the following way:

In a large wound of the thigh, in an excellent state of proliferation, well granulating, the granulating tissue was stripped over a certain extent. The stripped part was rolled into a sort of tube and fixed with sutures. At the end of a few days proliferating new tissue again covered the surface of the wound, forming a continuous layer. The latter had resumed its original condition. But several days later, after having removed the whole of the proliferating surface (for a secondary suture following the usual operative

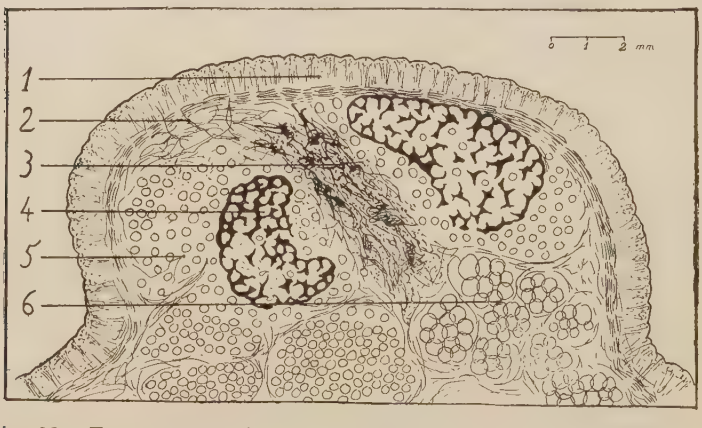

Fig. 33.—Transverse section of the ossified zone in the preceding experiment. *1*, granulation tissue; *2*, the subjacent fibrous bed; *3*, necrotic zone; *4*, new formed bone; *5*, muscular tissue cut transversely; *6*, adipose tissue.

method), we found in the portion of the wound which was rolled up in the form of a tube, a cylinder of true bone.

The experiment was not constantly successful with us. What at first astonished us was later found to be easily explained, when it was possible for us better to specify the fundamental factors of osteogenesis. This result was obtained only in wounds in the vicinity of bone lesions in process of repair. Change of connective tissue is essential (creation of an ossifiable medium), but it is also indisputable that calcareous materials should be present (local calcific surcharge).

Now, this last condition is realized in the case of a wound at the site of a fracture. Under the influence of the changes produced in the connective tissues by the experimental formation of a tube, there is a necrosis of a certain quantity of the tissue elements of the wound. To this tissue necrosis is added a calcareous reserve. We have here the usual case with heterotopic ossifications.

In these experiments it is impossible for the periosteum to have any effect. The site of the fracture is far from the surface of the wound. No relation is observed between the periosteum and the bone formation which is completely free and enclosed in a mass of granulation tissue.

Finally, if it were a question of periosteal action, there was no reason why it should wait on the formation of our tube of fleshy granulation tissue to manifest itself.

We believe that the formation of this experimental bone demonstrates in the clearest way the intervention of the factors which we have specified.

Moreover, in one case we have been able to utilize this process of osteogenesis to obtain the complete ossification of a bone cavity in a tibia. We filled it with a sheet of fleshy granulation tissue dissected in some convenient way. Bone appeared in it. At the end of six years, bone of good quality is everywhere present, definitely effacing the old cavity.

CHAPTER X

APPLICATION OF THE GENERAL LAWS OF OSSIFICATION TO PATHOLOGY

In the preceding pages there have frequently been questions of pathology. We have, in fact, studied normal osteogenesis above all with the aid of abnormal phenomena by considering disease and accident as experiments which introduced variable factors into the birth, architecture, and life of bone, and in this way rendered them more readily analyzable. Reciprocally, we have shown in multiple examples how the true mechanism of bone formation permits a better understanding of obscure pathological phenomena, because osteogenesis is a single phenomenon, and the organism always employs the same means to make and unmake bone.

In this way contemporary researches on rachitis have revolutionized our knowledge of the mechanism of ossification in showing us the capital importance of factors of which no one had dreamed. A few works in biochemistry have done more than almost a century of pathological anatomy.

But it is worth while to examine the general field of bone pathology from the point of view that we have developed: first in showing how, in a whole series of diseases, one can verify the laws that we have proposed, and second, in studying how these same laws lead to an understanding of pathological manifestations which are inexplicable without them.

But before proceeding further, it is necessary to recall the exact elements of our conception and it is important to keep them in mind.

1. Bone is a connective tissue modified by metaplasia, and this modification is governed, above all, by humoral

processes. Bone is not the result of a secretion by specific cells.

2. All new bone formation is due to a concomitant rarefaction either of bone or of calcified elements. Conversely, all rarefaction of bone or calcified elements can lead to new bone formation in the connective tissue in its vicinity.

3. After bone rarefaction, the fibrous tissue, freed of its calcareous impregnation, is susceptible of undergoing a series of evolutions which are normal to all connective tissue: fibrous, cartilaginous, etc.

4. Bone rarefaction is due to an augmentation of the blood circulation: there is no resorption without hyperemia. On the other hand, stasis of the interstitial fluids favors new bone formation.

Progress in the study of the diseases of bone is dependent on the question of definition. It is necessary to modify henceforth current pathological language. The usual terms are inadequate. There is no stopping of the employment of expressions which lack sense and which conduce to errors. From one country to another the terms have not the same signification at all. In advance of all reading it is necessary to fix the vocabulary of the authors, a thing which is often difficult. A complete revision of synonyms should be undertaken. The same remarks apply to the classification of bone diseases. At the present time this classification does not exist. While waiting for the power of defining bone diseases etiologically, it is important to group them according to mechanisms. That will avoid mistaking for the principal lesion that which is only a contingent phenomenon.

It is not yet possible for us to make this enormous revision. But we propose no longer to employ these physiologically false terms of fertile bone, sterile bone, periosteal sowing, bone graft, bone atrophy, rarefying and condensing osteitis. One is loath to abandon empty words to the sense of which one is accustomed, without dreaming that their

employment has contributed to the obscuring of problems which are obscure enough as it is. A great step will have been made when it is really desired to make the effort of speaking a language commensurate with our knowledge.

I. INFLUENCE OF HUMORAL FACTORS

Rickets is a disease governed by humoral factors. From the standpoint of ossification in general it offers the great interest of revealing the importance of normal biological factors which it is otherwise impossible to distinguish.

The rachitic subject is incapable of normally calcifying the pre-osseous substance which it forms. But up to the stage of calcification, ossification proceeds normally in him. The problem reverts to the determination of what interferes with calcification. Three factors condition the deposition of calcium:

1. An organic factor pertaining to diet; this is what is currently called vitamin, though there is nothing to permit the statement whether it is rather a substance than a property, or physicochemical behavior of an element normal in the diet; 2, light, the powerful rôle of which is still so mysterious; 3, a suitable balance between the calcium salts and the phosphorous compounds in the diet.

These are the primary factors which, from the practical point of view, permit control of the disease. Thanks to the knowledge we have of them, it is possible for us to provoke or arrest the disease at will.

On the other hand, we are ignorant of the intimate mechanism of their action. How does this mysterious fat-soluble factor come into play? How does light act, especially through its ultraviolet radiations? We have no idea on this subject. We are not even capable of forming an approximately admissible hypothesis which explains these effects.

We see more clearly how the quantities of calcium and phosphorus intervene. From the chemical standpoint os-

sification has as its basis a break in the equilibrium of phosphocalcium reaction.

The quantity of Ca taken in by alimentation is generally sufficient in man. The osteopathies of famine by deprivation of calcium are debatable. What is important is the relation between calcium and phosphorus.

This fact has been placed beyond doubt. No matter how large an amount of calcium is ingested in the food, it can be fixed in the bone only with the aid of the phosphate ion. It is phosphorus which governs the fixation of lime. Without phosphate, calcium is unutilizable. Inversely, if the phosphates are too abundant in the humors, there is remission into solution of the calcium fixed in the bone tissue. Intravenous injection of phosphate leads to a decalcification (Salvesen). A disease of the horse, "wheat disease" (la maladie du son), characterized by a loss of the calcareous materials of the bones, might be due to an excess of phosphates in the food.

We will note here a point we have nowhere found mentioned.

It is well known that in the course of the development of rachitic bone, there is not only insufficiency or absence of all calcification of the pre-osseous substance, but even exaggerated development of the latter. It is laid down in a much greater quantity than in the normal state, so much so that following remission and late calcification of this pre-osseous substance, the bone is hypertrophied, irregular.

We would willingly believe that these two phenomena, absence of calcification and hypertrophy of the pre-osseous substance, are allied. Pre-osseous infiltration has a general tendency to extension. It comports itself like an edematous infiltration. But the thing that arrests it is precisely calcareous infiltration. When the pre-osseous substance is calcified, it is in some way immobilized. It ceases to extend. Now, in rickets, when there is no calcareous infiltration, or when it is restrained (there is never absolute rickets), the

hyaline pre-osseous substance is laid down abundantly because its extension is limited only tardily and with difficulty. Between arrest of infiltration by pre-osseous hyaline substance and calcium deposition, there is an undoubted relationship.

II. RELATIONSHIP OF RAREFACTION AND NEW BONE FORMATION

All new bone formation in the vicinity of the skeleton is bound up with a rarefaction of neighboring skeletal parts, which always precedes it in time.

Consequently, when in a disease (for purposes of clearness we put tumors aside) one notes the formation of a mass of new bone, it is necessary to think that the essential thing in the bone affection is not the new bone, but a zone of rarefaction which is often unrecognized and to which generally little interest is given. It is quite unnecessary to attach any importance to the morphological appearances that the new-formed bone can take. It is not in this that one will find the cause of the disease. It is only a secondary phenomenon. One might almost say that the new-formed bone is not pathological. It is only a consequence, a result of the rarefaction.

To speak of subperiosteal osteitis, as has been done at times in the presence of diaphyseal rarefactions with peripheral osteogenesis, is evidently beside the question and puts the pathogenesis on a false basis. The thickness of the new bone does not in the least change matters. It is inevitably the case that in the zone of rarefaction the disease has its beginning. It is there that it is necessary to seek for the initial stages and the causes. And it is thus in all the cases of the same order.

Furthermore, it is necessary to understand this point well. There is no rarefying or condensing osteitis. These expressions should disappear. The process which causes

bone to resorb is never an osteitis: it is a vascular or humoral phenomenon.

From the standpoint of the relations between rarefaction and new formation one can distinguish two varieties of bone diseases. In some the new bone formation is important; there is bone reconstruction which is more or less disorderly; such are Paget's disease, Recklinghausen's disease, osteomyelitis, arthritis deformans (deforming rheumatism), ankylosis. In others the reconstruction is very slight, even existing only histologically; such are the false cysts of bone, diseases of callus, certain sarcomas of bone.

A. Diseases Characterized by Rarefaction Accompanied by Important Bone Reconstruction

Paget's disease, Recklinghausen's disease, leontiasis ossea, etc., are characterized by a rarefaction of the bone tissue, often intense, which may be generalized or, on the contrary, localized to a few bones. This rarefaction is still of an unknown origin. It is constantly accompanied by new bone formation around the involved bones. The latter are histologically atrophied, and at the same time anatomically hypertrophied. The clinical symptoms observed are in harmony with the coexistence of these two opposed processes. The bone rarefaction explains the enlargement, sometimes very great, of the Haversian spaces, the bone deformities, spontaneous fractures, epiphyseal separations, the radioscopic images, and the softness of bone which one can at times cut with a knife. The concomitant new bone formation explains the histological presence of coarse bone in the parosteal tissues, the hypertrophy so characteristic in certain bones (bones of the skull in Paget's disease, bones of the face in leontiasis ossea), and the deformations by osteophytes.

In osteomyelitis, the relationship of the rarefaction and reconstruction is more evident than elsewhere. The disease is complex because the initial processes dislocate the

phenomena which, in themselves, engender others on the spot. The last comers will have pathologically almost as much importance as those from which they are derived. They can even, in the attenuated form, reach the point of masking them completely.

From the point of view that interests us, the disease is reducible to this, the massive infection of the vessels and the cellular tissue of the connective tissue spaces of the bone, leads to a sudden extensive sequestration. While the dead bone slowly detaches itself from the living bone, the congestion and edema of the neighboring periosteum prepares it for ossification and the latter operates following the intense bone resorption which takes place at the line of junction of the living and dead bone.

As long as the dead bone is not removed or has not been expelled, as long as anatomical conditions prevent obliteration of the cavity, edema of the connective tissue and bone resorption continue. The peripheral bone attains considerable dimensions making the expulsion of the dead bone and the recovery from the disease more and more difficult.

This new-formed bone hence has considerable pathological consequences and, moreover, it is not diseased bone. It is very probable that it is not even infected. In connection with the acute phase of the disease, one might say that it is only an epiphenomenon, thrown into the periosteal tissue by a disease remote from the bone.*

The general mechanism of osteogenesis should even govern the comprehension of the phenomena which accompany the evolution of deforming rheumatism (arthritis deformans). Juxta- and intracapsular ossifications which one notes in it are but the sign of bone rarefaction: primi-

*Frequently in operating on cases of chronic osteomyelitis I have found minute walled-off abscesses in the involucrum which were considerably removed from any sequestra or areas which were obviously infected. Furthermore, on microscopic examination of newly formed bone from an osteomyelitic focus, one frequently finds that the young connective tissue between the newly formed trabeculae contains considerably more leucocytes than would be expected in noninfected tissue. In other words, it has been my experience that the newly formed bone in osteomyelitis is frequently diseased bone, and it is my belief that this is one of the reasons why this disease is so difficult to cure.—*J. A. K.*

tive phenomena which condition neighboring osteogenesis, secondary phenomena, exactly as are the deformities which are produced under the action of tendino-muscular forces. Singular as it may seem at first glance, the new bone formations are pathologically, we do not say clinically, without importance. They can teach us nothing on the determinism of the disease. They should be considered accessory and contingent.

On the other hand, granted that we do not know the mechanism of bone resorption, one should think that there is in the origin of deforming rheumatism a circulatory phenomenon, in a definite sense, everything being reserved as to the exact cause which precipitates it.

In bony ankylosis it is the same way. If clinically and functionally speaking it is intraarticular osteogenesis that is all important, biologically, the determining factor is a rarefaction of the epiphysis. The disappearance of the investing cartilage following the usual arthritis permits local calcific changes to take place in the intrasynovial fibrinous exudate. If the cartilage is simply perforated in one or two points, the union is at first irregular. If it is intact, the bone deposit is peripheral (circular ankylosis); the interior of the articulation is only tardily affected after the cartilage has disappeared.

This rarefaction of epiphyses is a constant phenomenon that radiography does not generally reveal, but which is well known to those who have operated on ankylosis: often when one wishes to break an ankylosis, it is below it, in the rarefied juxtachondral tissue, that the rupture takes place, and the spongy tissue of the epiphysis is always abnormally friable.*

*It has been my impression that the rarefaction of epiphyses encountered in ankylosed joints is due to atrophy of disuse. In operating upon ankylosed joints which have been subjected to approximately normal stress and strain I have not observed that the epiphyses were abnormally rarefied. As a matter of fact, in some ankylosed joints which have borne weight in a position of flexion over a considerable length of time, one finds that the epiphyses contain more dense bone than normal, this bone having been formed according to Wolf's laws to support the unusual strain.—*J. A. K.*

B. Diseases Characterized by a Rarefaction Accompanied by No or Insignificant Reconstruction

This group is complex. There are cases in which bone reconstruction does not take place because of local reasons. In other cases there are general conditions which prevent it.

In the first group are found the greater part of the diseases of callus. The first examples of it which can be given are the cystic calluses, or spongy calluses, in which a peripheral shell is formed around the enlarged bone cavities, extending beyond the diaphyso-epiphyseal line.

Their development is usually connected with general causes. It is not out of place to ask if there are not purely local causes which also come into play. We have said previously that the connective tissue does not push forward into liquid media and that when in certain fractures with great displacement an abundant encysted serous effusion persists in the neighboring muscles, callus cannot form in default of intrafibrinous connective tissue organization. There is perhaps in the origin of cystic callus a process of the same order. In the interfragmentary space a serous liquid (serum arising from the traumatic hemorrhage) is collected. There is only fibrin surrounding this collection. Thus there is formed a peripheral shell with a central area which is unossifiable because it lacks a fibrous matrix. That which tends to show that this is the case is that the polycystic callus is never seen except at the epiphyses and more especially at the upper extremity of the humerus; there traumatic crushing of the trabeculae can very easily produce a cavity in which the liquid encysts itself. It should be remarked that this liquid, placed in a condition where absorption is very difficult, at times augments, little by little, by exudation from the neighboring vessels, reaches a point where it pushes back the bone shell at the periphery, and mechanically atrophies it.

The condition called cystic osteitis should be connected with spongy calluses.

In this disease, where there is neither osteitis nor cyst, a more or less extensive cavity is hollowed in a bone, and this is full of a clear liquid that no wall of its own could secrete or allow to exude. In the published observations there is very frequently a traumatism at the beginning or in the previous history, but there is no fracture. On the contrary, it is frequently the case that some day a spontaneous fracture supervenes which is followed by complete recovery of the disease. Nothing from the beginning to the end of the evolution of this process allows one to dream of an infectious origin.* Albuminous osteoperiostitis due to very attenuated infection in no way resembles it. The process is not neoplastic. The temptation is great to ask whether there has not initially been an incomplete fracture, trabecular crushing, interstitial hemorrhage, or clot formation, the serum of which could not be resorbed and thus gave rise to the condition. The false metatraumatic cyst is an obstacle to bone repair, atrophy of neighboring bone which rarefies little by little through simple vascular phenomena, progresses up to the moment when a spontaneous fracture empties the cavity, brings the walls together, causes an interstitial hemorrhage, and allows the process of osteogenesis to unfold itself normally.

The rarefaction, whether posttraumatic or not, which is the origin of these cysts arises about equally through osteolysis and osteoclasis. When the latter is very accentuated, the whole zone in resorption shows numerous osteoclasts which are particularly voluminous. In general they are interpreted as myeloplaxes (megakaryocytes). This is an error. It is uniquely a matter of osteoclasts, that is to say of polycaryocytes (multinucleated giant cells),

*Phemister (Jour. Am. Med. Assn., 1926, vol. 87, 1429) has recently reported the isolation of streptococci from two cases of bone cysts. In two unpublished cases of my own I have isolated low grade staphylococci from cysts in bone which were typical clinically, roentgenographically, and histologically.—*J. A. K.*

cells with multiple nuclei, while the myeloplaxes (megakaryocytes) are cells with single branching nuclei. What comes into play are then cells of connective tissue origin, and not cells originating from the hematopoietic tissue.

These elements are sometimes so abundant that they give to the tissue which fills the cyst a characteristic appearance. It is easily understood how in these cases a predominant rôle has been attributed to them. However, their rôle is commonplace. These are the phagocytes, affecting the bone resorption rather than the red cells arising from the hemorrhage.

The presence of connective tissue cells filled with yellow pigment (hemosiderin) is an histological proof of the presence of interstitial hemorrhage, and, in consequence, is a secondary argument in favor of traumatic origin.

One can easily attribute to an effusion of blood and its difficult resorption the histological aspects shown by the fixed connective tissue cells in these cysts. They are voluminous and on first appearance present the aspect of those of sarcoma. Therein is a source of pathological-anatomical error to which many authors have drawn attention. It is especially easy to make such an error in a biopsy which gives information on only a very limited area in the specimen.

One sometimes finds trabeculae of young bone in these cysts. It might be said that in these cavities, excavated in ordinary Haversian bone, a true callus forms, which at times is rudimentary and scarcely calcified. This should not surprise us when we consider what we know of the ties that join bone rarefaction and bone formation.

This exact relationship of rarefaction and new bone formation allows the review in a special way of the bone or osteoid formation met with in sarcoma of bone and given as characteristic of osteosarcomas.

In the classical theory, these tumors represent osteoblastic sarcoma, due to a mild development of osteoblasts,

secretors of bone. This theory implies the idea of the specificity of osteoblasts. In spite of the convenience, it has the misfortune of being incorrect. The osteoblasts, far from being a secretor of bone, are in reality only commonplace connective tissue cells which struggle in some way against bone metaplasia.

Osteosarcoma is hence not an osteoblastoma. It is an ordinary sarcoma of the connective tissue spaces, in the depth of which are unfolded the phenomena of bone metaplasia, exactly as they take place in normal granulation tissue. This bone metaplasia is produced in proportion to and in the degree of the destruction of bone by sarcoma, in the same way that it occurs in the neighborhood of all foci of rarefaction.*

The trabeculae which are thus formed are not the result of a specific process. Their appearance depends on the juxtaposition of the local conditions usual to ossification.

One well understands, therefore, the irregularity of the distribution of the bone trabeculae in sarcomas. Following the examination of a specimen, the histological diagnosis will always be sarcoma, but with various adjective adjuncts: osteoid sarcoma, ossifying sarcoma, osteochondrosarcoma, etc. It is well known that the synonomy is rich. In truth, it is but a sarcoma in which are unfolded the processes of metaplasia.

Bone productions noted so often in chondromas and in chondroid tumors are explained in the same way. In the osteochondromas or the osteochondrosarcomas there is no cancerization; that is to say, simultaneous disorderly development of osteoblasts and chondroblasts. There is in reality bone metaplasia in contact with a cartilaginous mass which is in part necrosed and calcified. This is the known phenomenon of heterotopic ossification.

*It should be noted that metastatic bone sarcoma in the lung and far removed from any local bone focus may lay down extensive deposits of new bone. On the other hand, sarcoma arising from nonosseous connective tissue may produce large tumors in which no ossification occurs.—*J. A. K.*

One can find the counterproof of what we have just said in the fact that purely connective tissue tumors are capable of giving metastases with bone formation; Eugène Pollosson has recently reported a curious example of this.

III. EVOLUTIONARY POWERS OF THE CONNECTIVE TISSUE ARISING FROM RAREFACTION

The connective tissue freed by rarefaction does not remain inert. This is not its physiological custom. Under the influence of a series of conditions, local or general, humoral or mechanical, it undergoes various transformations which explain certain histological characteristics of the affections where rarefaction dominates.

In Paget's disease and in Recklinghausen's disease, the connective tissue of the spaces enlarged by rarefaction becomes fibrous. These affections have for that reason been called fibrous osteitis, a bad term, for there is no trace of inflammation. The word osteofibrosis would be preferable.

The freed connective tissue can undergo a chondroid transformation. This transformation is observed after certain traumatisms.

The freed connective tissue can take on the characteristics of granulation tissue with voluminous fibroblasts, but these cells are normal and without monstrous nuclei. This tissue is rich in blood capillaries, which are sources of abundant hemorrhages. Cavities of this kind are filled with a soft hemorrhagic substance which resembles fibrin.

These hemorrhages particularly put into play the phagocytic activities of the elements present (phagocytosis of red cells), and one encounters numerous giant cells, with multiple nuclei which are the elements mistaken for megacaryocytes (myeloplaxes). The cells of this granulation tissue are particularly large and active. Also they are

sometimes compared to sarcoma cells, whence the term of sarcomas with myeloplaxes is given to these lesions. And in the meantime, from the clinical standpoint they have nothing characteristic of sarcoma: a simple curettage cures them, provided it be complete. In reality these elements are not sarcomas and do not include myeloplaxes. They are only masses of very vascular granulation tissue, sometimes more or less infiltrated with leucocytes which enclose ordinary phagocytic giant cells.

These lesions would be much better named benign tumors with giant cells, than sarcomas with myeloplaxes, if it should be established that they really are tumors. But it is entirely likely that these affections are not tumors. This does not mean that they have an infectious origin. Their origin is actually unknown.

Connective tissue can undergo myxomatous transformation. It can also become malignant sarcoma. In this case, the connective tissue cells will take on the habitual monstrous characteristics. From the practical point of view, it is by the notation of these cells with huge nuclei and with abnormal mitoses that the histological diagnosis of sarcoma can be made. The presence of giant cells with multiple nuclei rests outside the elements of the diagnosis. It is allied to the relatively accessory process of phagocytosis, whether of bone elements or of red (blood) cells. These elements can be very numerous in a true sarcoma, where they are only contingent. Their presence has no particular prognostic significance. They are not in fact megacaryocytes (myeloplaxes), that is to say, elements of the hematopoietic system, but are only common giant cells with multiple nuclei and not with polymorphic giant nuclei.

One can conceive of the existence of tumors developed from the myeloid series, with true megacaryocytes. They are certainly rare tumors; we have never met with them.

IV. INFLUENCE OF AUGMENTATION OF THE BLOOD CIRCULATION ON BONE RAREFACTION

Every increase in the circulation of the blood results in bone resorption. This fact is beyond question. Examples of it are numerous. Its deeper mechanism is not yet defined. Perhaps it is a matter of a change in the local phosphocalcium balance.

On the other hand, circulatory increase certainly interferes with new bone formation. This is perhaps because blood acceleration suppresses or diminishes the stasis of the interstitial lymph, the necessary condition for all osteogenesis. One may suppose, however, that when the circulation is more active the interstitial lymph, surcharged with calcareous elements, is stirred up in such a way that the calcium deposition cannot take place. And in fact one sees that in certain recesses which appear to be withdrawn from similar influence, new bone formation takes place.

If we apply these facts of normal physiology to pathology, it may be asked whether a certain number of these diseases of indeterminate etiology, which are characterized by bone rarefaction, are not under the domination of simple vasomotor variation. If this hypothesis is true, one should be able to open, in nosography, the as yet inexistent chapter of the diseases of bone of vasomotor origin.

This is what is meant by the above.

There frequently exists osteoporosis, more or less localized or diffuse, which is developed after peripheral nerve traumata. These instances are observed especially in the small bones of the hand and of the foot, after an accident which has apparently not been serious. In a few weeks an "atrophy" of the bone, a decalcification, is visible on radiography. It is accompanied by pain and functional impotence, which at times are wrongly called traumatic arthritis. These cases are insufficiently known and very

badly described. We ourselves have given study to them in the last few years. To what do they correspond?

The affected bones are rarefied. We know that there is no rarefaction without hyperemia and that hyperemia can be accompanied by it. Now, on the other hand, all peripheral nerve traumatism is accompanied by a more or less lasting disturbance in equilibrium which begins with vasoconstriction and quickly turns into a vasodilatation, which the oscillometer clearly shows.

This is what we have called reflexes of the traumatized axone. Albert has shown that experimentation brings about this state in conditions which permit of no other interpretation.

In this connection one can imagine the following explanation, peripheral hyperemia by reflex of the axone and consecutive bone resorption. More obscure causes to explain the duration of the state which is called Sudeck's disease are not to be sought.

Here it may be properly asked whether a parallel mechanism is not the origin of certain singular syndromes which have been elevated to the dignity of specific bone diseases, such as the *tarsal scaphoiditis* of Koehler, the *traumatic malacia of the semilunar* of Kienbock, the *osteochondritis deformans of the hip,* Calvé-Waldenström-Legg-Perthes disease, and the vertebral deformities of Kümmel-Verneuil disease.

It is very probable that still other isolated localizations of this bone rarefaction of traumatic vasomotor origin will be found, and that other specific diseases will yet be diseases of X——— or of Y———.* One can say that from now on all will have the same character, an insignificant trauma or one distant in origin, an evolution which is slow, progressive, apyretic, accompanied by slight pains and resulting in final spontaneous curability, with at times definite

*Just recently osteochondritis of the knee and of the shoulder has been described.—*J. A. K.*

bone deformity and absence of all signs of inflammation. Up to the present, pathology has not taken account of the reflexes of the traumatized axone. Now that the intimate relation which unites vasodilatation and bone resorption is known, it is permissible to believe that the syndromes which they bring about should be frequent.

Among the bone diseases which seem to arise from a vasomotor disturbance, the most characteristic appears to be that called *otospongeosis* or *otosclerosis*. In this disease, which affects hearing so severely, there is in a primary phase bone rarefaction, that is to say, resorption, and in a second, bone condensation on the spot. Now, the disease most often supervenes in women with great vasomotor sensitivity of the face, subjects of sudden flushings and sudden skin eruptions, with delicate vasomotor equilibrium of the face. If one adds to the above that the disease generally begins during pregnancy, which compels the mother to draw on her reserves of skeletal calcium to construct her infant, one reaches a sufficiently physiological comprehension of a disease which one is pleased to call unknown in its essence and mechanism. At the moment when the organism exacts a call on the calcium reserves, it is withdrawn at those points where the circulatory conditions render this easier. In women with an unstable faciocranial circulation, the petrosal (or probably other bones of the skull, particularly the maxillae) gives up its calcium and otosclerosis is precipitated. This spongy petrosal would be of no consequence if the ear were not there, and if soon the local calcific transfer were not to take place in the chain of the ossicles by ankylosing them.

The notions of the normal physiology of bone which we have developed allow us to understand well the mechanism of this obscure disease.

Is it proper to put it on the same footing with osteomalacia? It does not seem that this is possible. But osteo-

malacia is still so veiled in numerous obscurities that we lack the fundamentals for studying the problem.

On the other hand, similar physiological explanations should come into play in the interpretation of singular bone states recently described, such as the ivory vertebra of Souques. Let us understand what is meant by that. Souques has shown that certain generalized neoplastic involvements of the vertebral column are manifested as a massive condensation of the vertebral bodies in which the outline of the bone is preserved intact, but which is condensed in mass like a vertebra of ivory and appears very dense on radiography. Sicard has studied similar cases.

Parallel processes appear to exist elsewhere in the absence of all neoplasia, and Nové-Josserand has reported a case of a very dense vertebra without any tumor to explain it.

How can this condensation of the spongy tissues of the vertebra be explained? It has seemed very mysterious. But if one states as a principle that all bone condensation presupposes a feebleness of effective circulation, all is explained. This is not simply because all dense bone is bone of little vascularity, but especially and above all because all hyperemia results in rarefaction.

How can this come about in the cases seen by Souques? The rare histological examinations practiced have shown that there was intra-Haversian penetration of neoplastic outgrowth.

Such penetration is not possible except following the destruction of the Haversian vessels, the Haversian canal being too narrow and too full for a neoplastic growth to invade it without destroying what is normally present there. It is probably because of the existing blood decrease that the vertebra condenses little by little.

The process ending in the formation of an ivory vertebra is in short absolutely identical with that which one finds in *hemicraniosis following meningeal tumors,* of which

Cushing, Phemister, and Penfield have reported typical examples. Phemister has shown elsewhere that certain metastases of bone could cover up the intra-Haversian type of infiltrations and that in these cases the bone condenses in twisted strata at the periphery.

In all anatomical states of this kind, unfortunately special attention has not been given to the circulatory conditions at the limits of the condensed bone. It will be necessary henceforth in similar cases that care should be taken to study this precise point, for it is there, in our opinion, that the key to the process will be found.

It is again through circulatory conditions that one should explain the rarefactions and new bone formations which are observed after certain nerve sections. It is curious to see that the destruction of certain nerves is rapidly followed by an intense decalcification, while those of another nerve present nothing, and that the experimental section of a certain number of trunks is without effect on the formation of a callus.

Bone disturbance is much more marked after section of the median, ulnar, or the internal popliteal of the sciatic nerves, than after that of the radial or the external popliteal of the sciatic. As it is established that these three nerves, median, ulnar and internal popliteal of the sciatic, are carriers of sympathetic fibers, it is permissible to believe that it is to the section of these fibers alone and to the vasomotor disturbances which result from it that the bone rarefaction noted is due.

By means of these disturbances through rarefaction one should attack, in spite of the contrary appearance, the periarticular osteogenesis described by Mme. Dejerine and Cellerier in paraplegics due to medullary section. As was natural in these cases, only abdominal ossification has caught the eye and fixed the mind of the observer. And it is in the function of this bone genesis that the disturbance has been described. In the meanwhile, radiography and

late anatomical examinations show that the neighboring epiphyseal bone is very much rarefied. From that time all becomes clear in the mechanisms of these abnormal productions. Section of the cord produces a peripheral vasomotor unbalance where vasodilatation predominates, and following which there is simultaneously edema of the periarticular connective tissue and bone rarefaction. These two phenomena, essential to ossification, being brought together in the same zone, osteogenesis follows. But one should not be deceived by this: true bone disturbance of nervous origin is the rarefaction of normal bone. The new bone formations are only its apparent evidence.

It is the same way, without doubt, in the tabetic arthropathies in which one sees placed side by side a marked edema of the periarticular soft parts, an intense rarefaction of the epiphyses and diaphyses and intra- and perisynovial new bone formation, while the oscillometer shows elevation of the arterial pressure and strong oscillations. We believe that the affiliation of these phenomena is the following: first, active vasodilatation; second, edema of the connective tissue and the resultant bone rarefaction; third, osteogenesis in connection with it. In short, the arthropathies are but the consequence of a vasomotor disturbance of innervation, itself dependent on existing radicular lesions or luetic lesions of the peripheral arteries which have affected the adventitia. Hence it is unnecessary to explain them by a complicated nervous mechanism; they enter quite naturally into the order of normal biological processes which precipitate the production of a usual vaso-dilatation at the periphery. They are, if one prefers, the normal consequence of a vasomotor irregularity in a definite sense.

CHAPTER XI

THE INFLUENCE OF SOME PHYSIOLOGICAL PRINCIPLES ON THE FUTURE OF BONE SURGERY

The exact knowledge of the intimate mechanism of osteogenesis should influence the general comprehension of the therapeutics of surgical bone diseases and of methods of technic which are suitable for the treatment of these conditions.

If one considers that the surgery of ablation and of drainage, that is to say that of tumors, of sequestra, and of infections, calls for no special procedure, and that orthopedic surgery is above all mechanical, one becomes convinced that true bone surgery, the surgery specifically of bone, is uniquely that which sees one or the other of these three objectives: to lead to the production of bone, to prevent the resorption of bone, to control new ossification. Does it truly exist?

One can only advance suggestions in this direction. Surgery is still too imperfect to be able to give complete solutions of those things of which it stands in need. But it is interesting to state the problem and to trace a program of studies.

A. Can One Influence the Formation of Bone?

To obtain bone, it is necessary to prepare a suitable connective tissue which will be the matrix for it and to furnish to this tissue the necessary calcareous materials.

It is not forbidden to think that a day will come when we will be able, one the one hand, to influence the connective tissue by vascular or nervous agencies, by endocrine extracts, or by pharmacodynamic means, and on the other hand to supply the fibrous matrix with the necessary phosphocalcific substances in a directly assimilable form.

But up to this actual moment, we have but two ways of making bone: the sub-periosteal method of Ollier and bone transplantation.

The sub-periosteal method of Ollier when it is rigorously applied, detaches from the bone the favorable connective tissue medium, represented by the periosteum, and the calcareous material which supplies the bone chips loosened by the sharp periosteal elevator.

It has been frequently said that it is not applicable to healthy bone. It is certain that Ollier scarcely utilized it except on bones already in advanced process of resorption due to common infections or to tuberculosis, and in these conditions the technic which he recommended was easy, the elevator, without one even wishing it, detaches flakes of bone with the periosteum. But on the normal bone it appears to be usable only with difficulty, as is currently said. In fact, as we showed in 1917, it is very easy to reach an identical result by going farther with small repeated movements which strips the bone in lines which are perceptible to the fingers and visible to the eye, which leave on the deeper aspect of the periosteum, seed of powdered bone, fulfilling the same end and having the same outcome as the chips detached by chance from diseased bone.

In this way, thanks to a technic adapted to conditions of hard bone and which had not up to that time been described, intraperiosteal bone regenerations have been obtained with perfect regularity of form, every time that no intercurrent infection interfered with the experiment. We have given numerous examples of this in animals and in man. They will be found collected in the thesis of Jean Haour.

One can certainly, then, with the method of Ollier, thanks to modifications we have made of it, cause bone to form at will. However, it is necessary for that purpose that one has in place healthy connective tissue and resorbing bone. When these conditions are not realized, the only possibility

that one has of securing bone regeneration is given by the autoplastic transplant of a bone removed by known technic. When the transplantation is operatively successful and no obstacle is placed in the way of the complex unfolding of the biological phenomena which we know, a bone is reconstructed which finally totally integrates in the original mould.

This result is very remarkable. But there are so many contingencies current in the biological evolution of a transplant that it is permissible to ask whether one could not obtain it as well, with more chance of success and more security, by abandoning the exact idea of a graft and having recourse to the implantation in the tissues of nonresorbable prosthetic pieces. We know that they are susceptible to union with healthy bone and can remain in the tissues and be tolerated for an indefinite period. The question would merit being systematically worked out.*

B. Can One Influence Bone Resorption?

The problem is difficult because we do not yet know in all their details the determinants of resorption. We know only that it is conditioned by a circulatory overactivity and that is all.

Now, it is difficult to regulate the blood flow at will. In an entirely empirical way one can today consider it as established that periarterial sympathectomy at a distance modifies the régime in a definite way. In fact, it is followed experimentally with a rapid ossification in fractured zones and, clinically, of a reossification of regions in too active resorption where there is no utilization on the spot of the free materials.

In man, in the delays of consolidation, in failure of consolidation after osteosynthesis, or in the course of the reconstruction of a graft, periarterial sympathectomy is

*See note on page 179.

followed by rapid formation of bone. But in other conditions, it appears to make bone tissue enter into resorption because of the excessive hyperemia which it brings about.

With all the reservations which the insufficiencies of our knowledge impose in a study scarcely sketched, one may say that periarterial sympathectomy precipitates bone resorption and thus permits ossification, but that these phenomena can pass beyond bounds. Events take place as if there were for the preservation of bone an optimum of circulation which the operation modifies in a direction which is always the same, but in a quantity that we do not yet know how to proportion.

It is necessary to add that sympathectomy acts by simultaneously creating an ossifiable connective tissue medium fit to receive the materials freed by the resorption. By this, in short, it provokes the necessary conditions for the formation of a callus.

In any case, the fact is there. From now on one has the means of influencing bone resorption and, in a certain measure, rendering it utilizable to our proper ends.

C. Can One Model New Ossifications?

There still remain many things to be understood before one can dream of directing the functional adaptation of bone. And meanwhile we have seen that the architectural organization of bone is entirely dominated by mechanical influences which orient the trabeculae in predetermined directions. Likewise, it is established that a frail fibrous barrier suffices to change the orientation of the trabeculae. Hence there is certainly the theoretical possibility of modelling ossifications, of directing them in a useful way and of obtaining, if this is not a too ambitious expression, the skeleton that one desires. This is at least the line along which future works should be undertaken if one wishes to

attain to a true guidance of the ossifications of which the organism has need.

An entirely new chapter of bone surgery will exist when this program will have been completed. It is then that we can enter upon the treatment of diseases which, for the time being, we limit ourselves to observing, without being able to do anything to check them.

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